

May 17, 2007

R. Rodney Howell, M.D.
Chair
Secretary's Advisory Committee on Heritable Disorders
and Genetic Diseases in Newborns and Children
Professor
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Re: The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children nomination and evaluation process for candidate conditions on the uniform newborn screening panel.

Dear Dr. Howell:

As investigators and clinicians working to develop treatments and cures for Spinal Muscular Atrophy ("SMA") and to provide care for SMA patients, we write to urge the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children ("Advisory Committee"), to consider permitting the addition of disorders for which a treatment or cure is not presently available to the uniform newborn screening panel. Specifically, the Advisory Committee is encouraged, as it develops a nomination and evaluation process for candidate conditions, to state explicitly that the existence of a treatment or cure is not a determinant factor in whether a disorder is eligible for inclusion in the uniform screening panel. Further, in establishing the responsibilities and operating principles of an external Evidence Review Group ("ERG") to advise the Advisory Committee on the acceptability of a disorder for universal newborn screening, the Advisory Committee is urged not to require the ERG to consider the existence (or lack thereof) of a treatment or a cure as a limiting factor.

SMA is the leading genetic killer of children under the age of two. While there is no treatment or cure available at the present time, there have been several exciting research breakthroughs over the past five years. Newborn screening holds tremendous promise to assist in the development of a treatment and/or cure for SMA.

We believe that SMA-related research, clinical trials, and drug development can benefit from identifying affected individuals at birth. For the following reasons, these efforts will be significantly enhanced if pre-symptomatic SMA-afflicted children can be identified through newborn screening:

1) Natural history data indicates only a small opportunity for intervention in the most common and severe form of SMA.

It is estimated that SMA occurs in about 1 of every 6,000 births. Approximately 50 to 70 percent of affected children suffer from Type I SMA, the most severe form of the disease. More than 95% of these children die in infancy or require extensive respiratory support by their second birthday. Dr. Kathryn Swoboda, Associate Professor of Neurology at the University of Utah School of Medicine, has conducted electrophysiologic studies in infants demonstrating normal distal innervation during the pre-symptomatic phase of the disease (Annals of Neurology, 2005 May, 57:704-12). However, in infants with SMA type I, rapid loss of motor units occurs in the first three months, and severe denervation with loss of more than 95% of units has occurred by six months of age. Therefore, a very small window for beneficial

therapeutic intervention exists in infants with SMA type I, and therapies will need to be administered early for maximum benefit.

2) Preliminary data in human and mice models indicates that pre-symptomatic drug intervention is more effective than post-symptomatic.

Dr. Charlotte Sumner has found that compounds that function as HDAC inhibitors have been shown to increase survival and improve motor function in SMA mouse models, which indicates that it should be possible to find drug-like compounds that can do the same in humans (Journal of Clinical Investigation, 2007 March, 117(3):659-71). Dr. Swoboda has preliminary treatment data from a cohort of infants who were diagnosed pre-symptomatically in the newborn period due to a history of an older affected sibling. Thus, these infants began treatment in the first few weeks of life. In one case, an infant predicted to develop type I SMA was able to achieve the ability to sit unsupported by 9 months of age. In the entire cohort of six children treated to date, each has fared better than their affected siblings historically, sometimes substantially so, suggesting that drug therapy and other interventions administered early may provide therapeutic benefit, even for infants with Type I SMA. These preliminary results provide the first evidence in support of the hypothesis that disease course can be modified in SMA patients with early intervention. More extensive data obtained from SMA mice models by Dr. Arthur Burghes, Professor of Molecular and Cellular Biochemistry at Ohio State University, also indicates that pre-symptomatic drug administration is a key component to successful treatment of SMA.

3) Pre-symptomatic enrollment into clinical trials may greatly enhance the chance of identifying an effective drug intervention for SMA, particularly for Type I SMA infants. Clinical trials in symptomatic patients with end-stage denervation and contractures may actually disprove efficacy of therapies which, when administered early, might truly benefit this population.

While the findings of Dr. Swoboda, Dr. Burghes, and others with regard to pre-symptomatic drug intervention are promising, additional studies to confirm such benefit can occur only if an adequate population of pre-symptomatic Type I SMA infants is identified for participation in clinical trials. We believe that newborn screening will facilitate interventions to modify disease severity and progression. Additionally, it represents a critical component in ensuring early enrollment of patients in therapeutic trials to ensure optimal benefit from promising new treatments.

In addition to the benefit to research related to SMA, diagnosis of SMA at birth will allow patients to obtain proactive treatment earlier in the disease progression with regard to nutrition, physical therapy, and respiratory care. This will lead to a better quality of life for SMA-afflicted children.

Early intervention does not have to be limited to drug therapy. Many SMA infants show progression in the setting of nutritional compromise. If identified early, this problem could be managed proactively via nutritional interventions. Furthermore, given the availability of non-invasive respiratory treatments for SMA patients, such as the use of a cough machine to help facilitate the clearing of secretions, earlier implementation of such interventions will improve quality of life, reduce respiratory morbidity, and extend lifespan. Additionally, newborn screening will provide parents with earlier genetic counseling before they are likely to have a second affected child, which frequently occurs when diagnosis is delayed.

In general, the natural history of SMA appears to be changing due to more proactive care and improved clinical management. Earlier intervention through newborn screening could enhance these results further to the benefit of SMA patients and the health care system. A delay in diagnosis has significant economic implications in addition to the medical consequences. Moreover, identifying SMA-afflicted individuals at birth eliminates the pain and cost of unnecessary testing that otherwise would take place in attempting to diagnose the affected patient. While the rationale for early intervention for SMA infants is compelling,

the promise of compounds that could rescue at-risk motor neurons prior to onset of disease symptoms makes the argument even more persuasive.

In addition to the aforementioned items, the case for implementing universal newborn screening for SMA is made more convincing by the fact that the technology to conduct newborn screening for SMA currently exists. Dr. Thomas Prior, Professor of Pathology and Neurology and Director of Molecular Pathology at Ohio State University, has developed a DNA technology using Real-Time PCR for effective newborn screening of SMA from blood spots. This assay has greater than 95 percent sensitivity and 99 percent specificity. The Prior Lab has now developed a luminex platform for SMA newborn screening, which is both highly sensitive and more efficient. Furthermore, it has been adapted for the use of bloodspots.

Due to the evidence discussed above, we believe that the Advisory Committee should permit the addition of disorders to the universal newborn screening panel even in the absence of a demonstrated treatment or cure. We strongly urge the Advisory Committee not to preclude an external ERG from considering the case for universal newborn screening of a disorder solely due to the lack of a presently available treatment or cure.

Newborn screening can play a vital role in the development of such a treatment or cure and in improving the quality of life of the infants afflicted by deadly and disabling disorders such as SMA. The SMA community, and other similarly situated communities, should be allowed to make the case during the nomination and evaluation process for candidate conditions on the uniform screening panel.

Sincerely,

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