TESTIMONY

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RE: Nomination of Krabbe Disease

Hi. My name is Joanne Kurtzberg and I am a Pediatric Transplant physician at the Duke University School of Medicine. For the past 3 decades, I have studied treatment of patients with leukodystrophies, lysosomal storage diseases, and inherited metabolic diseases with hematopoietic, also known as, blood stem cell transplantation. The goal of this therapy is to replace the patient's blood and immune system with donor cells producing normal enzyme which is missing in the patient. In addition, enzyme producing microglial cells are replaced in the brain. We know that this therapy corrects enzyme levels in the blood and has variable penetration in the central nervous system. After transplant, as long as full engraftment is achieved, normal blood enzyme levels are observed for life.

In Krabbe disease, where both the central and peripheral nervous system systems are affected, transplant rescues the central nervous system, but is less effective in the peripheral nervous system. In addition, in infantile disease, transplantation is most effective if performed in the first 3-6 weeks of life. This both justifies and challenges newborn screening for Krabbe disease.

As you know, NBS for KD has evolved over the past 2 decades. Thanks to the outstanding and courageous work of Dr. Joe Orsini and his team in the New York State NBS lab, Dr. Mike Gelb at UWA, and Dr. Dieter Matern at the Mayo clinic, the algorithm for NBS for KD has been developed and optimized. Today, the application before the Advisory Council for Heritable Disorders in Newborns and Children to add Krabbe disease to the RUSP reflects over 2 decades of work which has allowed us to (1) define the best testing algorithm for use in NBS for KD, and (2) define the core disease to target.

Fortunately, the 3rd time KD was presented to the ACHDNC on January 30, 2024, it was approved for addition to the RUSP. By way of history, the first nomination in 2009 was not approved because of problems with low specificity of the testing algorithm, a high incidence of false positive results, and disappointing outcomes of HSCT in the initial patients identified with IKD in New York State. By 2021, when KD was renominated for the core condition of early and late infantile disease, the testing algorithm using a GALC screening assay followed by reflex (or second tier) testing of Psychosine in screen positive samples had been implemented in some states and was shown to have high sensitivity and specificity for diagnosis of infantile Krabbe disease, but lower specificity for later onset KD. In addition, the benefits of transplant in babies with Infantile Krabbe Disease, that is disease with onset of clinical symptoms in the first 12 months of life, were published and show to be significantly improved over prior reports, although it isn't clear that this was appreciated by all of the reviewers. However, identification of babies with a risk for later onset Krabbe disease was not as specific and resulted in notification of risk to some families were, in reality, a risk was not present. Concerns related to these issues expressed by some of the reviewers led to a tie vote -which is a negative outcome.

Infantile Krabbe Disease was renominated for additional consideration in August of 2024. This was done for several reasons. First, we know that diagnosis of KD through NBS is the only way to rescue affected

babies from the pain, suffering, and early death associated with infantile Krabbe disease. It also prevents parents from undergoing months of suffering with their babies while experiencing long diagnostic odysseys only to learn the diagnosis at a time when it is too late for treatment. We know that transplant is beneficial for these babies and strongly believe that parents are entitled to learn about their baby's diagnosis and options for treatment in the newborn period. So, what was different about the third and successful nomination and how did we improve it over the prior ones? First, we narrowed the core disease target to infantile Krabbe disease where results of NBS are clear: that is, the GALC screen is low and psychosine is $\geq$10nM. Second, we include in this nomination, the clear recommendation that the testing algorithm should consist of a GALC screen followed by reflex (or second tier) testing of psychosine in all screen positive cases. With this approach, the rare baby with IKD can be diagnosed in the first week of life and referred for consideration for HSCT today and, maybe gene or other therapies, in the future.

I want to spend a minute dispelling myths about HSCT for infantile Krabbe disease. First, I know that HSCT is not the final answer and that it is not perfect, but it dramatically improves the survival, function, and quality of life outcomes of babies with IKD. It is the first of what I believe will be a series of steps leading to continuous improvement of the effective therapies for this disease. I know, as a hematologist oncologist that if we had stopped treating children with Acute lymphoblastic leukemia 30 years ago after the first drugs produced remissions only lasting 3 months, we would not be curing 80% of children with ALL today. Progress in the treatment of challenging diseases is incremental, but one has to start in order to succeed. Second, I know that no babies are transplanted without evidence of active clinical disease which is present on neurophysiologic and imaging studies of babies with IKD in the first few weeks of life. Third, I know that the preparative regimen, high dose chemotherapy, does not cause the peripheral neuropathy associated with Krabbe disease. I know this because I have transplanted many other young infants for congenital immunologic or hematologic diseases using the same chemotherapy and these children do not have peripheral neuropathy post-transplant. Lastly, I know that rapid referral for evaluation and treatment of newborns with IKD is possible if the proposed testing algorithm and a prospective roadmap for rapid referral and treatment is in place.

In summary, NBS for Krabbe Disease saves lives. It also significantly improves quality of life for these babies and their families. In the past seven years, 51 babies were born in states who were not screening for KD and these 51 babies had no chance. Now Infantile Krabbe disease has been approved by the ACHDNC to be added to the RUSP. It is time for your state to vote in favor of adding IKD to your newborn screening panel to improve the lives of affected babies and their families.