Hunter's Hope Foundation

Krabbe ~ Leukodystrophies ~ Newborn Screening

March 3, 2023

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

RE: ACHDNC's vote on the nomination of Krabbe disease for addition to the RUSP

Dear Mr. Secretary:

As members of the ACHDNC's Krabbe Disease Newborn Screening Technical Expert Panel and nominators to add Krabbe disease to the Recommended Uniform Screening Panel (RUSP), we are writing to request that you expeditiously take action to provide the deciding vote on the nomination to add Krabbe disease to the RUSP. At the recent ACHDNC meeting on February 9, 2023, the committee's vote on the inclusion of Krabbe disease on the RUSP was a tie and the ACHDNC chair quickly proclaimed that this would have to be interpreted as a negative outcome. We disagree with this decision for the multiple reasons outlined below, ranging from the exclusion of critical evidence to serious procedural inconsistencies. In addition to the egregious missteps documented below, the community was appalled by the ACHDNC's general tone of unfounded negativity and disrespect to patients with Krabbe disease and their families.

For context, Krabbe disease is a severe neurological disorder that causes extreme impairments and death, typically by the patient's second year of life. Early detection of the disease through newborn screening, coupled with treatment prior to symptom onset, significantly and effectively leads to a longer life without many of the impairments typically associated with Krabbe disease. Newborns in New York State have been screened for Krabbe disease since 2006. Since then, 9 other states (including 1 prospective pilot study) have included this condition on their screening panels, accounting for 30% of all U.S. newborns. In 2008, Krabbe disease was nominated to the RUSP but following evidence review was rejected. In early 2010, the ACHDNC provided the nominators with a request to address three knowledge gaps identified as (1) the definition of Krabbe disease, (2) the testing strategy for screening and diagnosis, and (3) the benefit of treatment and its timing for the various forms of Krabbe disease. For more than a decade, the patient community worked closely with the disease's medical and scientific experts to meticulously address the issues raised. These gaps have been addressed and led to the re-nomination of Krabbe disease in 2021[1].

Our concerns with the recent meeting are as follows:

- In contrast to previous discussions of nominated conditions, the State Readiness Survey was not presented by an APHL representative but was minimized and very briefly touched on by Dr. Kemper, thus depriving the committee of critical information. However, this survey, if it had been presented, would have provided more explicitly the fact that 10 states, corresponding to 30% of the U.S. newborn population, already screen for Krabbe disease, and that the CDC's Newborn Screening Quality Assurance Program (NSQAP) has been supporting those programs with

reference materials and proficiency testing schemes since ca. 2013. Moreover, the committee did not learn that states already screening for other RUSP conditions (Pompe disease and Mucopolysaccharidosis type I) using tandem mass spectrometry can easily add the reagent to screen for Krabbe disease. Indeed, states that purchase the NeoLSD screening kit from PerkinElmer, Inc., the primary supplier of newborn screening equipment and reagents, only need to make changes to the data acquisition software because the NeoLSD kit includes reagents for 6 lysosomal enzymes (including for Krabbe disease), not only those needed for Pompe disease and Mucopolysaccharidosis type I. This information would have avoided concerns raised by some committee members about the readiness and cost of adding Krabbe disease to existing newborn screening programs.

- The committee liaisons to the Evidence Review Group, Drs. Kwon and McCandless, presented their assessment of the evidence review and initially categorized Krabbe disease in the ACHDNC's decision support matrix as a "C1." For reasons that are unclear to everyone in the patient community, their report appeared more concerned with an outdated screening process that was in place in 2009 prior to drastic improvements implemented with the addition of psychosine measurement as a second-tier test.

    - Concern was raised about unnecessary harm to families that are challenged with false positive screening results. While a valid concern raised during the first evidence review in 2009, this concern is significantly mitigated by the proposed screening strategy which was first employed in Kentucky. As is well known, eight of the 10 states screening for Krabbe disease are now using psychosine which minimizes and nearly completely avoids false positive screening results[2]. Additional states, such as South Carolina beginning as early as May 2023, will emulate the Kentucky approach where two patients were identified and successfully transplanted (out of state) at 24 and 30 days of life; among 380,000 babies screened in Kentucky there have been zero false positive results to date (personal communication, Kentucky Department for Public Health).

    - Moreover, the committee members made false statements regarding critical evidentiary facts. The goal of newborn screening for Krabbe disease as clearly stated in our nomination package (but not considered in the presentation by Drs. Kwon and McCandless), is to identify babies at risk for developing Krabbe disease in the first 3 years of life as the "core condition." This population of babies is identified through screening of GALC activity with psychosine as a second-tier test. Newborns with infantile Krabbe disease (symptom onset before 1 year of age), show low GALC activity and very high psychosine levels (>10 nM; normal <2 nM). Those with slightly later onset (up to 3 years of age), have low GALC activity and intermediate psychosine levels (2-10 nM). Given that this represents more than 70% of individuals affected with the disease, statements made during the discussions prior to the vote about newborn screening detecting a lower percentage of infantile cases are false. Relevant data are published, were included in the draft report of the evidence review, and in Dr. Kemper's presentation. Yet, Drs. Kwon and McCandless decided to emphasize the first eight years of screening for Krabbe disease as published by the New York program in 2016, before

New York added psychosine as a 2nd tier test in 2022. Current data on this subject was not brought to the full committee. We heard from countless providers and families who were dumbfounded by the conclusions drawn by Drs. Kwon and McCandless because they did not adequately represent the advancements made in newborn screening for Krabbe disease.

- Concern was raised about the possibility of transplanting an infant unnecessarily. This is a uniquely theoretical concern as there is no evidence such has ever happened in the context of Krabbe disease. Indeed, transplant criteria and guidelines are published (included in our nomination package) and when followed leave no room for such a sentinel event to occur.

- On other critical issues, the committee heard outdated evidence that was inconsistent with the nomination package. Concern was raised about the outcome of hematopoietic stem cell transplantation (HSCT), currently the standard of care. Again, Drs. Kwon and McCandless focused on results of HSCT reflecting the initial New York experience (2006-2014) in 5 babies (including 1 pair of siblings), and essentially ignored more recent and published results in 9 babies diagnosed through NBS in the past 6 years, all of whom are surviving and doing well.

- A 12-year-old child, diagnosed with Krabbe disease because of a family history and treated with HSCT in the first few months of life, and who even has a Nike sneaker named for him[2] eloquently testified and provided living proof of the benefit of newborn screening, but was essentially disregarded. Additional reports and the data from HSCT in babies identified because they had a sibling with Krabbe disease were understated at best. While HSCT is not a cure, it clearly extends and improves the lives of babies/children and families with Krabbe disease. This is documented in the nomination package that includes support for screening and early treatment by more than 3,000 patients and families, as well as by public comments made during the meeting. Moreover, without a positive family history or newborn screening, patients with infantile forms of Krabbe disease are diagnosed after the onset of symptoms, when HSCT is no longer an option. The evidence review's statistical modeling is clear in its assessment that without newborn screening these patients will suffer greatly until they die in childhood. As one mother accurately stated in her public comments to the committee, "Krabbe without early diagnosis has no chance of survival. Newborn screening gives our kids a chance of treatment and the chance to live…"

- During the discussion following Drs. Kwon and McCandless's report, committee members had several questions about the screening strategy currently employed by various screening programs, about treatment outcomes, and about the logistics of getting affected babies to transplant centers. However, no attempt was made to get answers to these questions from non-voting members of the committee. Nevertheless, a committee member made the motion to elevate the categorization of Krabbe disease in the decision support matrix from "C1" to "B1" because of the actual evidence of higher certainty of benefit of newborn screening for affected patients. The committee voted in support of this motion. But after the vote to reclassify Krabbe disease to "B1", no additional discussion was allowed, essentially depriving committee members of critical information.

- Procedural concerns:
  - Per the original charter for the ACHDNC[3] published in the Federal Register, the committee is supposed to have an odd number of members, up to 15. The committee currently has only 14 members[4] for reasons that have not been disclosed.

  - In contrast to previous ACHDNC meetings, the organizational representatives were explicitly told by the chair that they would not have the opportunity to ask questions or provide comments during the final session. Indeed, several questions raised by committee members during the discussion were left unanswered although either one or more of the organizational representatives or even experts in the audience, including those of the evidence review group, could have provided answers. No justification was given why the representatives were not allowed to participate in the discussion. Instead, the discussion was rushed even though most members, including the chair, pointed out the difficulty of coming to a decision. We are aware that several representatives were taken aback and requested continuation of the discussion at the next meeting followed by another vote. Overall, this meeting was in stark contrast to the deliberations - witnessed by one nominator and former committee member (Matern) - on the addition of previous and similar conditions, such as Pompe disease (May 2013), Mucopolysaccharidosis type I (February 2015), and Spinal Muscular Atrophy (February 2018) when committee members sought and immediately received answers from experts in the audience.

  - The last three conditions added to the RUSP (Spinal Muscular Atrophy, Mucopolysaccharidosis type II, and GAMT deficiency) were categorized in the decision support matrix by the committee as "B2" because clinical benefit was deemed of moderate certainty and implementation of screening by laboratories required new resources. Because it takes relatively little effort for public health laboratories to add Krabbe disease to their screening programs and because of the moderate certainty of benefit from early treatment, the committee voted to move Krabbe disease to a "B1". However, there was no discussion following the elevation of Krabbe disease to "B1" especially in the context of the favorable decisions made about these previous 3 lower scoring (B2) conditions.

Since the committee's decision on Krabbe Disease in 2009, the Hunter's Hope Foundation has been contacted by the families of 136 U.S. children who were not screened for Krabbe disease at birth, and therefore, were not given the opportunity to receive treatment for this deadly disease. Without an explanation of why Krabbe disease was clearly treated differently by the ACHDNC than previous conditions, the patients and families affected by Krabbe disease and other rare conditions will lose faith and trust in the ACHDNC. More importantly, U.S. children will continue to suffer and die from a treatable disease unless they are born in one of the 10 states already screening for Krabbe disease.

Given the above reasons, ranging from the exclusion of critical evidence to serious procedural inconsistencies which took place at the February 9 ACHDNC meeting, we respectfully request you expeditiously review what took place and take decisive action to approve the nomination of Krabbe

disease to the RUSP, also because the recommended screening approach would prevent false positive results. Children with Krabbe disease yet to be born in the U.S. deserve the opportunity to live. We are happy to provide additional information as requested.

Sincerely,

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Note: Dr. Maria Escolar was part of the original group that nominated the condition in July 2021 but has recused herself given her new role at Forge Biologics, which currently has a gene therapy trial for Krabbe disease underway.

1. 2021 Nomination Package for Krabbe Disease: https://drive.google.com/file/d/1_qfd7zmG6ZY6ZFBcEKQOro5QKLNb-M42/view?usp=sharing
2. https://ohsufoundation.org/stories/freestyle-2022-michael-wilson/ (last accessed 3/2/2023)
3. ACHDNC charter: https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/acdnc-charter.pdf (accessed 3/2/2023)
4. ACHDNC Membership: https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/achdnc-membership-roster.pdf (accessed 3/2/2023)