Hunter's Hope Foundation
Krabbe ~ Leukodystrophies ~ Newborn Screening

July 22, 2023

Dear Dr. Calonge,

On behalf of every child affected by Krabbe Disease, their families, and the Krabbe Disease community at large, we are writing to submit a revised nomination to add Infantile Krabbe Disease as a "core condition" to the Recommended Uniform Screening Panel (RUSP).

Since our previous and broader nomination of infantile and late infantile Krabbe Disease (KD) failed by a tie vote earlier this year, we have met with you and others to determine the best way to ensure that newborn screening (NBS) identifies babies with the most common and rapidly progressive form of KD so they are provided options for treatment in a timely fashion, and to also ensure that unaffected newborns and their families are spared the psychosocial and emotional stress of false positive NBS results.

Based on the concerns and recommendations from committee members and HRSA, we are amending our nomination from infantile and late infantile Krabbe Disease to infantile Krabbe Disease (IKD), characterized by rapid symptom onset before 12 months of age. From a NBS perspective, IKD is defined by significantly reduced galactocerebrosidase (GALC) activity and psychosine (PSY) ≥10 nM in the newborn blood spot. Restricting the nomination to IKD eliminates ambiguous diagnoses, uncertainty about possible later onset disease, and allows for a clear pathway for management of newborns with IKD.

After reviewing screening practices and outcomes from 11 NBS programs which implemented screening for KD over the past 17 years, it is evident that IKD, can be definitively diagnosed through NBS based on first tier testing of GALC activity, followed by second tier testing for PSY where a PSY concentration of ≥10 nM in the NBS dried blood spot sample would trigger immediate follow up. The data shown in the table below are limited to those of 7 states screening for KD that already use PSY as a second tier test. Ohio, New Jersey and South Carolina were excluded from this review because the former two do not yet have a two-tier strategy and rely solely on GALC activity, and South Carolina started NBS for KD only recently (5/15/2023). The Indiana NBS program did not provide the requested data.

The nominated strategy is highly specific with all infants with PSY ≥10 nM having active KD, **resulting in zero false positive cases**. This strategy, which enables rapid diagnosis and referral, is critical because babies with IKD require treatment decisions before clinical symptoms develop to achieve the best possible clinical outcomes. While

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molecular testing could further inform future family planning and afford a deeper understanding of the disease, we emphasize that molecular testing should not be part of the newborn screen or delay referral of a baby with IKD (PSY ≥10 nM).

The cost of implementing our nominated screening strategy would be minor, especially compared to other conditions added to the RUSP since 2009. This is because states that screen for the RUSP conditions Pompe disease and Mucopolysaccharidosis type I (MPS I) using a commercial screening kit (NeoLSD from PerkinElmer) already measure GALC activity in every NBS sample and are already paying for the necessary reagents. Just turning on the relevant functionality in the acquisition software would reveal the GALC activity in every analysis performed for the two other RUSP conditions. The additional cost would be second tier testing for psychosine which, however, is necessary for only a fraction of newborns (ca. 0.04%; see Table). No additional personnel should be required by NBS programs using the NeoLSD kit given the small number of second tier tests required and the overall prevalence of KD (ca. 1:240,000 live births, see Table) which would result in only 0 to 1 abnormal case per year in most states.

Table. Number of true and false positive results modeled per the nominated NBS strategy for infantile Krabbe disease (reduced GALC activity and PSY ≥10 nM**)**.

State	GA	IL	KY	MO	NY	PA	TN	TOTAL
# of births	219,399*	770,000	404,626	216,000*	517,514	262,619	228,000*	2,618,158
Time period	9/2021-6/2023	12/2017-12/2022	2/2016-6/2023	4/2020-5/2023	1/2021-6/2023	5/2021-5/2023	7/2020-5/2023	n/a
# of PSY tests (% of total screened)	50 (0.02%)	426 (0.06%)	128 (0.03%)	336 (0.15%)	37 (0.01%)	44 (0.02%)	17 (0.01%)	1,083 (0.04%)
True positives	1 IKD	5 IKD	2 IKD	1 IKD	0	1 IKD	1 IKD	11^
False positives	0	0	0	2[#]	0	0	0	0
FPR	0%	0%	0%	0.001%	0%	0%	0%	0%
Prevalence	1 : 219,400	1 : 154,000	1 : 202,300	1 : 216,000	n/a	1 : 131,300	1 : 228,000	1 : 238,014

FPR, false positive rate; PSY, psychosine; *total number of live births was not provided by state and therefore calculated for the given time frames from: Hamilton BE et al. Births: Provisional data for 2019. Vital Statistics Rapid Release; no 8. Hyattsville, MD: National Center for Health Statistics. May 2020. Available from: https://www.cdc.gov/nchs/data/vsrr/vsrr-8-508.pdf; ^parents of two IKD cases declined HSCT; [#]samples from the two false positive cases were tested for PSY at Mayo Clinic on the same day. PSY was above the analytical measurement range for both, an unusual finding. Given the importance of rapid follow up of IKD cases, results were reported, including concerns about their accuracy. Analysis of blood spots from the same NBS samples in another laboratory

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yielded normal PSY. The families were informed of the confirmed laboratory error 3 days after follow up was initiated. A sentinel event investigation uncovered that the samples must have become contaminated in the laboratory with PSY standard used to prepare calibrators.

We want to reassure the committee that all cases of IKD identified by NBS (see Table) were subsequently evaluated by neurodiagnostic testing (MRI, EEG, BAER, VEP, NCT, CSF protein) and found to have signs of active disease on combinations of these studies. Thus, no baby has been transplanted without evidence of IKD and all babies with PSY ≥10 nM had signs of active KD (Page KM et al. Benefits of newborn screening and hematopoietic cell transplant in infantile Krabbe disease. *Blood Adv*. 2022; 6: 2947-56). Additional questions regarding the benefit of early treatment have been published and were responded to in detail in our previous correspondence, particularly of April 19 and May 30, 2023 (see attached). Moreover, families are supported in their decisions, including the option of palliative care.

In summary, we are submitting the nomination of IKD to be added to the RUSP as a core condition. This revised nomination addresses all concerns expressed at and after the committee's meeting in February 2023. Specifically:

- Identification of babies with IKD, who have 100% mortality without treatment, gives them (their parents) the option for treatment which extends and improves quality of life.

- All babies identified through this screening strategy will have IKD and the diagnosis and disease status can be confirmed within 7-10 days.

- No baby with IKD will be transplanted without active disease because all babies with a positive NBS referred for HSCT will be evaluated with extensive testing prior to treatment. It is also known that all babies with IKD have signs of active disease on neurodiagnostic testing in the first weeks of life.

- No baby will be exposed to long term monitoring or potential harm due to inconclusive NBS results.

We submit this revised nomination with the hope that IKD will be considered for expedited review by the Advisory Committee for Heritable Disorders in Newborns and Children. We anticipate a favorable response and are available to answer any questions.

Sincerely and with hope,

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