The Virginia Newborn Screening Advisory Committee's Report to the State Health Commissioner and Virginia Board of Health on the Addition of Krabbe Disease to the Virginia Newborn Screening Panel

December 29, 2020

Background to Commissioner's Charge

During the 2020 General Assembly Session, HB97 (Patron: Delegate Jason Miyares) was introduced proposing the addition of "…Krabbe Disease and all other lysosomal storage disorders for which a screening test is available…" to the Virginia Newborn Screening Panel. The proposed language was to be added to the Code of Virginia, specifically section 32.1-65. The estimated fiscal impact was $3,551,838 for Year 1 and $3,379,838 each year thereafter. HB97 was amended with a substitute, which required the Virginia Department of Health (VDH) to initiate a review of Krabbe Disease and provide recommendations to the Board of Health regarding whether Krabbe Disease should be included on Virginia's newborn screening panel. The substitute bill was adopted and passed in both the House and the Senate.

Section 32.1-65 of the Code of Virginia states that "every infant who is born in the Commonwealth shall be subjected to screening tests for various disorders consistent with, but not necessarily identical to, the uniform condition panel recommended by the U.S. Secretary of Health and Human Services and the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children" (ACHDNC). For future reference in this document, the uniform screening panel is also known and referred to as the Recommended Uniform Screening Panel (RUSP).

The specific screening tests that are included in Virginia's panel are defined in the Virginia Administrative Code 12VAC5-71-30 *Core Panel of Heritable Disorders and Genetic Diseases*. Currently, the Virginia newborn screening regulations cover 31 of 33 dried blood spot (DBS) disorders that are included in the RUSP. The remaining two disorders of the 33 DBS disorders on the RUSP, spinal muscular atrophy (SMA) and X-linked adrenoleukodystrophy (X-ALD), are currently in the regulatory process to be added to Virginia's core newborn screening panel with implementation planned for 2021.

Section 12VAC5-71-30 also outlines the process by which disorders are added to Virginia's panel. This process requires disorders being considered for addition to Virginia's core panel to be reviewed by the Virginia Genetics Advisory Committee (VAGAC), also known at this time as the Virginia Newborn Screening Advisory Committee. This process results in a formal report to the Board of Health through the State Health Commissioner. VDH staff informed Delegate Miyares of this process at the start of the 2020 General Assembly Session.

Historical Notes to Adding Krabbe Disease to National and State Newborn Screening Panels

A. Krabbe Screening Review by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)

The ACHDNC received a nomination of Krabbe Disease, specifically Early Infantile Krabbe Disease (EIKD) for inclusion in the Committee's RUSP for state newborn screening programs in 2009. The Committee conducted a study of the disorder and included evidence from the State of New York (NY), which had initiated screening for Krabbe Disease in 2006 and is still actively screening. According to the Committee's report (https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/previous-nominations/krabbe-27-june-2018.pdf), NY uses mass spectrometry as the primary method for Krabbe Disease screening. An initial positive screen is followed by three re-tests, and may be followed by a secondary DNA test if the average of these re-tests is ≤12% of the daily mean (below acceptable limits). In all cases, additional laboratory testing is needed to determine if a child is at low, medium, or high risk of developing the Disease.

The Committee reported that the expenses associated with testing in NY included startup costs of approximately $1,000,000. New York conducted 727,000 screens at $0.39 per baby, for a total of $283,530. Additional enzyme testing was completed for 50 babies at $250 per test, for an additional $12,500 per year. The required DNA testing for the 236 babies amounted to $153,400 ($650 per newborn). There was no estimate available from NY regarding medical work-up costs. After conducting its study, the ACHDNC determined that it would not add Krabbe Disease to the RUSP.

The ACHDNC identified the following evidence gaps in their letter to the Secretary:

> *1) Consensus about the case definition of what constitutes Early Infantile Krabbe Disease (EIKD)*
> *2) There is a need for additional information about the testing algorithm for EIKD. It is important to ascertain whether testing for Krabbe Disease would be a stand-alone test or done with multiplex testing, in part because of the cost implications.*
> *3) More information is needed about the specific benefits of Hematopoietic Stem Cell Transplant (HSCT) to treat patients and what mutations would benefit most from HSCT.*

B. VDH 2015 Review of Krabbe Disease Workgroup

During the 2015 General Assembly Session, two bills were introduced, HB 1420 (Sponsor Plum) and SB 835 (Sponsor Edwards), both proposing the addition of "…Krabbe Disease and other lysosomal storage disorders…" to the Virginia Newborn Screening Panel. After receiving an explanation of the process by which a disorder is added Virginia's newborn screening panel, Senator Edwards requested, in a letter dated January 26, 2015, that the Commissioner initiate a review of Krabbe Disease and make formal recommendations for or against addition to Virginia's newborn screening panel.

An expert workgroup of stakeholders was convened on May 5, 2015 to review scientific evidence of Krabbe Disease and provide a recommendation on adding Krabbe Disease to Virginia's newborn screening panel. The 2015 Krabbe Disease workgroup did not recommend the addition of Krabbe

Disease to Virginia's newborn screening panel. The workgroup felt strongly that the Virginia Newborn Screening Program (VNSP) should remain consistent with federal recommendations and that the data and unproven clinical options did not support the use of newborn screening for Krabbe Disease. Specifically, the review demonstrated:

- There is a lack of clear consensus on what exactly constitutes Early Infantile Krabbe Disease (EIKD);
- The current screening for Krabbe Disease is complex, expensive and has a low positive predictive value (PPV);
- The only currently available treatment for Krabbe Disease is not curative, has limited benefits, and carries high risk for morbidity and mortality. To be effective, this treatment must be initiated before the onset of symptoms. Thus, there is a high risk of exposing infants who do not have the disease to these high morbidity and mortality risks; and
- The high rate of false positive screening results will lead to significant psychological distress and a medical odyssey in attempting to confirm or refute the diagnosis.

VDH 2020 Krabbe Disease Review

A. Virginia Newborn Screening Advisory Committee Krabbe Disease Workgroup

A workgroup of the Virginia Newborn Screening Advisory Committee (NBS AC) was formed in response to passage of HB97 during GA 2020. The workgroup members represented the VDH, the Department of General Services (DGS) Division of Consolidated Laboratory Services (DCLS), medical experts of multiple professions from all major medical and higher education institutions within the Commonwealth, parents of children affected with Krabbe Disease, an out of hospital birth provider, and a general NBS parent advocate. The workgroup meetings were recorded in order to enhance the authenticity of meeting minutes.

A series of three workgroup sessions to conduct a review of Krabbe Disease were held on July 29, August 6, and September 2, 2020 with the following workgroup members:

- William G. Wilson, MD, Genetics and Metabolism, University of Virginia (UVA)
- Jamie Fraser, MD, Genetics and Metabolism, Children's National Medical Center (CNMC)
- Jullie Rhee, NP, Neurology, CNMC
- Hind Al-Saif, MD, Clinical Genetics and Metabolism, Virginia Commonwealth University (VCU)
- Jennifer Lent, Genetic Counselor, Clinical Genetics and Metabolism, VCU
- Brianna Murray, Genetic Counselor, Genetics, Children's Hospital of the Kings Daughters (CHKD)

- Abraham Segres, Vice President of Quality and Patient Safety, Virginia Hospital and Healthcare Association (VHHA)
- Kim Pekin, Certified Practicing Midwife (CPM), Clinical Director, Premier Birth Center
- Jana Monaco, Parent Advocate on Newborn Screening Advisory Committee and Advocacy Liaison of the Organic Acidemia Association (OAA) and National Organization for Rare Disorders (NORD)
- Dragan and Lana Grujicic, Parents of child with Krabbe Disease
- Kasey Feldt, Parent of child with Krabbe Disease

The following VDH and DGC/DCLS staff were in attendance:

- Christen Crews, MSN, RN, Public Health Nurse Supervisor, NBS DBS Program, VDH
- Jennifer Macdonald, MPH, BSN, RN, Director, Division of Child and Family Services (DCFH), VDH
- Heather Board, MPH, Acting Director, Office of Family Health Services (OFHS), VDH
- Robin Buskey, Policy Analyst, OFHS, VDH
- Emily Hopkins, MS, Director of Laboratory Operations, DGS/DCLS
- Denise Toney, PhD, Laboratory Director, DGS/DCLS
- Leigh Emma Lion, MS, Newborn Screening Group Manager, DGS/DCLS
- Paul Hetterich, MS, MBA, SM(ASCP), MB(ASCP), Newborn Screening Group Manager, DGS/DCLS

VDH program staff compiled information for workgroup members and created an online resource tool of on demand content. All workgroup members were provided access to the website and were asked to review the content prior to the first workgroup session on July 29, 2020. The website content included a background of the 2015 VDH Krabbe Disease workgroup review; overview of Krabbe Disease (pathophysiology, forms, incidence, diagnostic testing, and treatment); documents related to the 2009 RUSP review; summary of the 2015 VDH Krabbe Disease review; other state newborn screening program experiences; potential fiscal impact; and 26 journal articles. Workgroup meeting recordings were uploaded to the website after each session for future reference. The VDH 2020 Krabbe Disease review website is located at https://covgov.sharepoint.com/sites/VDH-KrabbeReview2020-External, and access can be requested by emailing Christen Crews, VDH NBS Public Health Nurse Supervisor, at christen.crews@vdh.virginia.gov. VDH program staff consulted with the Krabbe Disease advocates, including parents in the workgroup and Hunter's Hope Foundation, to provide current journal articles and arrange for Krabbe Disease experts to present to the workgroup.

The following Krabbe Disease experts participated as guest speakers:

- Amy Waldman, MD, Medical Director of the Leukodystrophy Center, Pediatric Neurologist at Children's Hospital of Philadelphia
- Maria Escolar, MD, MS, Director, Program for the Study of Neurodevelopment in Rare Disorders, University of Pittsburgh

- Joanne Kurtzberg, MD, Pediatric Bone Marrow Transplant Specialist, Duke Children's Hospital & Health Center
- Michael Gelb, PhD, Professor and Boris and Barbara L. Weinstein Endowed Chair in Chemistry, University of Washington
- Dietrich Matern, MD/PhD, FACMG, Co-Director, Biochemical Genetics Laboratory, Mayo Clinic College of Medicine
- Joseph Orsini, PhD, New York Newborn Screening Program

B. Krabbe Disease Pathophysiology

In the United States, it is estimated that Krabbe Disease affects about 1 in 250,000 individuals (19). Krabbe Disease is an inherited, degenerative disorder of the central and peripheral nervous systems and can be classified as both a leukodystrophy and a lysosomal storage disorder. There are approximately 50 other diseases that are also classified as lysosomal storage disorders. Krabbe Disease is specifically caused by mutations in the galactosylceramidase (GALC) gene. Over 70 GALC gene mutations have been identified and are attributed to Krabbe Disease.

While the age of onset and progression of Krabbe Disease varies, the disease most often presents in infants with onset before the age of six months (16), categorized as EIKD. Other categories of Krabbe Disease variants occur as late infantile (LIKD), juvenile/adolescent or adult onset (LOKD) and may progress more slowly (13, 19). The symptoms of EIKD include irritability, muscle weakness, feeding difficulties, episodes of fever without any sign of infection, stiff posture, and slowed mental and physical development. As the disease progresses, muscles continue to weaken, affecting the infant's ability to move, chew, swallow and breathe. Affected infants also experience vision loss and seizures. Death usually occurs before the age of two years (13, 16).

Screening and diagnosing EIKD can be complex and challenging due to the large number of possible GALC gene mutations and the unpredictability of disease course (13, 16). There is no cure for Krabbe Disease. Generally, treatment for the disorder is symptomatic and supportive. Dietary or enzymatic treatment has not been effective in either reversing the symptoms or halting disease progression and, therefore, is not considered an efficacious treatment option (13). Hematopoietic stem cell transplantation (HSCT) from umbilical cord blood, following myeloablative chemotherapy prior to the onset of symptoms, has been shown to stabilize the disease, although gross motor skills may still be affected by the disease and later onset of peripheral neuropathy may occur.

C. Krabbe Disease Workgroup Scientific Review

The workgroup completed a detailed review of a study published in 2019 evaluating the progression of Krabbe Disease in infants with symptom onset prior to 6 months of age (3). Of the 88 children in the study, 13 were asymptomatic and the remaining 75 were symptomatic at diagnosis. The median age of symptom onset was 4 months and the median age of diagnosis was 6 months, which was too late to improve outcomes. The majority of the babies who were asymptomatic at diagnosis were siblings of affected children or prenatally diagnosed. Diagnostic testing showed that both CSF

Protein and psychosine (PSY) levels were elevated in all infantile cases. PSY is a highly cytotoxic lipid that accumulates in the nervous system in the absence of the GALC enzyme. If a baby did have a positive newborn screen with a high PSY, it was recommended to refer to a transplant center immediately as opposed to waiting for confirmatory results (i.e. sequencing). An elevated PSY has been shown to predict EIKD.

The initial symptoms described in the study included a clinical presentation of irritability, feeding difficulties, spasticity, reflux, developmental delays, and poor weight gain (*Figure 1*). Myelination starts at around 26 weeks of gestation and a very severe form of EIKD could have "in utero" demyelination and present as symptomatic at birth. It is thought that most babies are born asymptomatic.

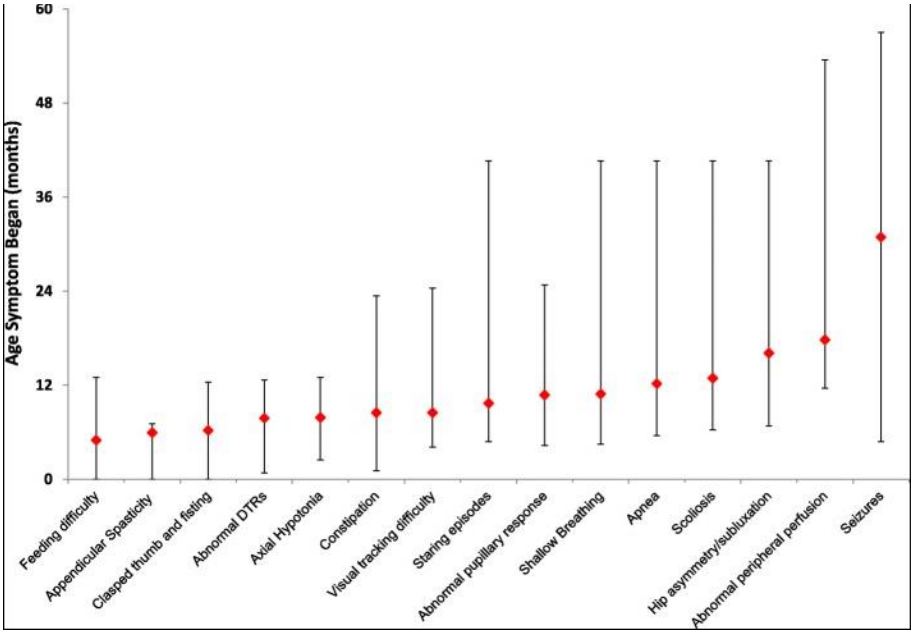


Figure 1: Ages at which common symptoms appear in children with Krabbe Disease. The red diamond represents the median age at which the symptom began. The lines show the minimum and maximum ages that the symptom began (3).

The guidelines for treatment of Krabbe Disease are recommended by age of onset of symptoms. Those with laboratory findings consistent with infantile-onset Krabbe Disease are candidates for hematopoietic stem cell transplantation (HSCT) before age 30 days, and the earlier the transplant, the better the outcome for the child. Dr. Kurtzberg advised that treatment is not advisable once clinical manifestations of symptoms occur. The successful transplant halts disease progression but does not reverse existing damage. Dr. Escolar stated that long-term outcomes for transplanted affected Krabbe children has shown that only one HSCT is needed in an affected Krabbe child's lifetime. Peripheral neuropathy has been found in transplanted older children with Krabbe Disease, and it is possible that gene therapy could improve outcomes in the next few years. There are no treatment facilities for pediatric HSCT transplants available in Virginia.

The outcomes of Krabbe Disease after HSCT transplant were reviewed by the workgroup. In one study from 2005, it was observed that infants who were transplanted prior to 30 days of life would have better

outcomes with a higher chance of more normal activity, mobility, communication and feeding (10). The study evaluated 25 Krabbe Disease infants (11 asymptomatic and 14 symptomatic at time of transplant) for engraftment, survival, and neurodevelopmental function. The study found a 100% survival rate if HSCT occurred pre-symptomatic and a 40% survival rate if symptomatic at time of HSCT with poor outcomes.

Several of the Krabbe Disease experts spoke about the recent improvements to newborn screening for Krabbe Disease with the inclusion of PSY in the testing algorithm. Seven of the nine states currently screening for Krabbe Disease have incorporated PSY testing as a second tier, or reflex test, and this results in rapid identification of EIKD. One challenge to identification and treatment of Krabbe Disease is the phenotypic variability of the disorder. The level of GALC deficiency identified by screening and the GALC mutations correlate poorly with the phenotype. Gene sequencing or mutational analysis can take several weeks for results, and this methodology was not recommended due to the time sensitivity with identifying EIKD cases. Dr. Matern informed the workgroup that biochemical second tier tests, such as PSY, increase the efficiency and effectiveness of NBS for Krabbe Disease, since the genotypes of Krabbe have too many "variants of uncertain significance (VOUS)."

The following risk stratification utilizing psychosine as a second tier was proposed by Dr. Kurtzberg:

- PSY > 10 nmol/L: High risk EIKD, refer immediately to transplant center
- PSY 2-10 nmol/L: Possible LOKD, requires long-term follow-up and monitoring. Additional time for diagnostic testing for risk assessment (i.e. gene sequencing)
- PSY < 2: unaffected, no additional follow-up

D. Krabbe Disease Screening in Other States

The states currently screening for Krabbe Disease include Illinois, Indiana, Missouri, Kentucky, New Jersey, New York, Ohio, Pennsylvania, and Tennessee. New Mexico, Louisiana, and South Carolina have legislation pending for the addition of newborn screening for Krabbe Disease. Program staff contacted screening states to obtain Krabbe Disease data, and staff utilized data provided by the states at the 2020 Hunter's Hope Symposium on Krabbe Disease. The information was also provided as a resource to the Krabbe Disease workgroup on the dedicated website.

The Kentucky NBS program has screened 243,693 babies for Krabbe Disease with 1 positive EIKD diagnosis. The program contracts with the Mayo Clinic to perform several newborn screening tests. The Mayo Clinic uses PSY as a second tier test for Krabbe Disease, and KY has not had any false positive results. The KY EIKD infant at 2.5 years of age has delays in gross motor development (sits alone, can walk/stand with assisted devices), normal cognitive development, and some spasticity in lower extremities.

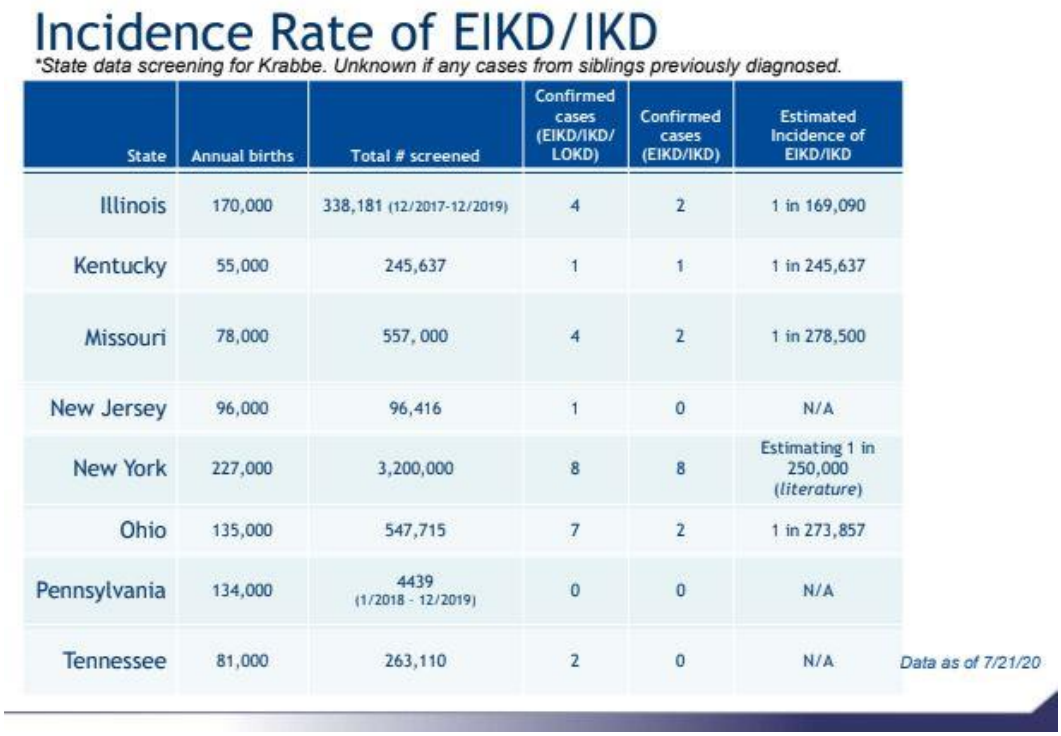
In Pennsylvania, testing is currently not mandated statewide. Dr. Waldman stated this was due to discussions on whether scientific evidence supported universal screening. Pennsylvania hospitals have the option to "opt-in" for screening and only one hospital, Hershey Medical Center, has elected to

screen for Krabbe Disease. No positive cases have been detected through newborn screening. Legislation was recently passed in 2020 to mandate universal screening in Pennsylvania for Krabbe Disease.

In New Jersey, routine screening for Krabbe Disease began in 2019. There have not been any positive EIKD babies detected.

The New York NBS program began screening for Krabbe Disease in 2006, and the state screens for approximately 250,000 infants annually. Dr. Orsini advised that the NY NBS laboratory screened with a single enzyme assay until 2016 and reported on PSY as a possible biomarker in 2013. A previous published study covering eight years of program data showed that out of 1.9 million infants screened, 620 screened positive and 348 were identified with Krabbe Disease causing variants. Of the 348, five were classified as EIKD, and Dr. Orsini advised that these infants had mainly poor outcomes. The NY NBS program updated their algorithm in 2018 to include PSY for rapid referrals and reflex to gene sequencing (second tier). Since 2018, approximately 560,000 infants were screened using the new algorithm. The program detected 45 presumptive positive screens, and 40 were referred to genetics with one or more disease causing variants. Of the 45 positive screens, 20 had elevated PSY and were classified as follows: 23 risk LOKD, 15 low risk EIKD, and 8 high risk EIKD. The NY NBS program has outsourced PSY testing to the Mayo Clinic, and the program noted a high number of babies with PSY >2; however, they are investigating to determine if this increased rate is population specific. The NY NBS program identifies approximately 30-50 babies annually with abnormal GALC enzyme.

Dr. Kurtzberg advised the workgroup that six infants have been identified by NBS programs in four states (IL, KY, OH, and TN) as having low GALC enzyme activity on the NBS and elevated PSY. HSCT was recommended and the median engraftment age was 13.5 days. At a mean age of 34 months, the transplanted children have some motor disability and all are progressing in language and cognition. The children's families reported feeling very positive about their child's transplant. When queried by a workgroup member, Dr. Kurtzberg was unable to definitively state the number of the six infants that were detected solely through newborn screening and not from prenatal or diagnosis of an affected sibling. In response to program staff outreach to the states, only the Kentucky Newborn Screening Program confirmed having an EIKD case identified solely by newborn screening (*Figure 2*).



Incidence Rate of EIKD/IKD

*State data screening for Krabbe. Unknown if any cases from siblings previously diagnosed.

State	Annual births	Total # screened	Confirmed cases (EIKD/IKD/ LOKD)	Confirmed cases (EIKD/IKD)	Estimated Incidence of EIKD/IKD
Illinois	170,000	338,181 (12/2017-12/2019)	4	2	1 in 169,090
Kentucky	55,000	245,637	1	1	1 in 245,637
Missouri	78,000	557, 000	4	2	1 in 278,500
New Jersey	96,000	96,416	1	0	N/A
New York	227,000	3,200,000	8	8	Estimating 1 in 250,000 (*literature*)
Ohio	135,000	547,715	7	2	1 in 273,857
Pennsylvania	134,000	4439 (1/2018 - 12/2019)	0	0	N/A
Tennessee	81,000	263,110	2	0	N/A

Data as of 7/21/20

Figure 2: Data as of 7/21/2020 by state as compiled by NBS program presentations at the 2020 Hunters Hope Symposium

A Krabbe NBS Council was recently created to provide guidance to all physicians of children identified by newborn screening for Krabbe Disease. The group meets monthly and is focused on improving follow-up protocols and education provided to patients with EIKD or at risk of developing LOKD. The Krabbe NBS Council includes Krabbe Disease treatment teams, members of the New York Krabbe Disease NBS consortium, representatives from each state currently screening for Krabbe Disease, and researchers studying NBS utilizing GALC and PSY. The historically referenced Krabbe Disease screening and algorithms have been updated with data to improve outcomes from the NY newborn screening program. Dr. Kurtzberg stated that the initial risk assignment of “positive” was thought to be too broad and identified babies not affected by Krabbe Disease with frequent, invasive follow-up and poor compliance. Criticism was received regarding use of these historical algorithms for unnecessary testing on unaffected infants. The Krabbe NBS Council is in the process of preparing a publication that provides expert consensus for the clinical guidelines of treatment for EIKD and the management of children who are at risk of developing LOKD. The new Krabbe Disease NBS guidelines will recommend all NBS programs utilize PSY for rapid identification of EIKD, risk stratification for LOKD, and reduction of false positives in newborn screening. The Krabbe NBS Council has a workgroup currently applying to the ACHDNC for reconsideration of Krabbe Disease to be added to the RUSP.

E. Screening Methodology

Eight of the nine NBS laboratories in the United States currently screen for Krabbe Disease by measuring the GALC enzyme activity in the dried blood spot (DBS) as the first tier test with tandem mass spectrometry. The GALC assay requires an overnight incubation. It is recommended that PSY be utilized as the second tier test for timely diagnosis of EIKD and reduction of false positives. Currently, five of the nine states screening for Krabbe Disease use PSY testing as the second tier test. It was estimated by Dr. Gelb that outsourcing PSY testing would cost approximately $100-300 per test and that Virginia would have approximately 10-20 babies per year with abnormal GALC enzyme needing reflex to PSY analyses.

F. Infrastructure Needs in Virginia

The process for setting up Krabbe Disease screening in Virginia would be a multi-year project. The DGS/DCLS and VDH program staff identified the following infrastructure needed by VNSP to screen for Krabbe Disease:

1. Transition of current testing for lysosomal storage disorders (Pompe and MPS-1) from microfluidics to tandem mass spectrometry
    a. Equipment needed includes, but is not limited to:
        i. Mass Spectrometers
        ii. Liquid Handlers
        iii. Centrifuges
        iv. Nitrogen Generation Equipment
        v. Reagents (an annual cost)
        vi. Equipment Maintenance support (an annual cost);

2. Additional space and environmental modifications at DCLS;

3. Additional program and testing FTEs at DCLS and VDH to conduct project planning, set-up and validate the chosen screening methodology, plan and develop educational resources, create follow-up algorithms and reporting documents, and conduct ongoing actual laboratory screening.

4. Application development to incorporate Krabbe Disease screening results into the current laboratory information management system (LIMS) maintained by DCLS.

5. Incorporation of new education module specific to Krabbe Disease screening into current educational website (newbornscreeningeducation.org) and continued maintenance of the website to maintain free access to Virginia medical providers.

6. Identification of a specialized medical support system within the Commonwealth for infants and their families who require specialized follow-up, diagnosis, genetic counseling and treatment of Krabbe Disease.

G. Economic Evaluation

Currently Virginia does not have sufficient funding or capabilities to screen for Krabbe Disease. The VNSP is funded solely through the collection of fees from the dried blood spot specimen kits sold to submitting facilities statewide, and the current fee is $138.00 per card. This fee was last raised on October 1, 2019 due to the anticipated addition of spinal muscular atrophy (SMA), X-linked adrenoleukodystrophy (X-ALD), and targeted congenital cytomegalovirus (cCMV) screening. With the infrastructure needs identified above, it is estimated that start-up costs in the first year of a Krabbe implementation project would be approximately $2,100,000.00 and subsequent years would require $2,007,000.00 annually.

It estimated that a fee increase of $18.59-$20.07 (*Figure 3*) would be required to cover the costs of adding Krabbe Disease to the Virginia Newborn Screening Panel. This increase would support the infrastructure needs identified by the group listed in Section F.

Testing Algorithms	Start-up Costs	Fee Increase	Minimum TAT for Results
MS/MS Screening ONLY	$1.9M	$18.59	3 days
MS/MS Screening Psychosine (2nd tier)	$1.9M	$18.70	8 days
MS/MS Screening + Psychosine (2nd tier) Molecular (3rd tier)	$2.1M	$20.07	22 days
MS/MS Screening Psychosine + Molecular (2nd tier)	$2.1M	$20.07	17 days

Figure 3: Estimate of costs to implement Krabbe Disease screening in Virginia, by potential methodology and testing algorithms. "TAT"= turnaround time

H. Workgroup Discussion of Krabbe Disease

After review of the most recent published literature regarding Krabbe Disease, presentations by the Krabbe Disease experts, and data from NBS programs in other states, workgroup members engaged in discussion regarding screening for Krabbe Disease in Virginia, as seen from their unique perspectives. Discussions were held at the virtual workgroup sessions, which were recorded. The concerns and discussion were compiled for review (*Table 1*).

Table 1

Concern	***Discussion Points***
Krabbe Disease is not on the ACHDNC Recommended Uniform Screening Panel (RUSP)	• Krabbe Disease does not fit the accepted criteria that have been in use since 1968 for determining the disorders for which universal newborn screening should be offered. • This condition has been thoroughly reviewed at the national level and the ACHDNC has not recommended that Krabbe Disease be added to the RUSP. • Gaps in evidence from the 2009 ACHDNC committee report still exist. • Virginia historically has conformed to the core disorders listed on the RUSP for the newborn screening panel. • The Krabbe NBS Council has formed a workgroup that is in the process of applying to the ACHDNC for reconsideration of Krabbe Disease to the RUSP work.
By adding Krabbe Disease to the Virginia newborn screening panel, current testing methodologies would need to be modified in DCLS.	• Adding Krabbe Disease to the Virginia panel would add costs to the lab and to follow-up, and this cost would either be passed on to the hospitals or a self-pay family with newborn infant- or would need to be budgeted by the legislature.
Fiscal impact should be considered	• Historically costs for newborn screening increases have been passed down to hospitals without increase in reimbursement from insurance. • If there is a public health benefit to testing, requesting general funds should be considered. • NBS was once funded by general funds, but is now fee-for-service. • Cost to state and public insurance sector for positive screened patient's diagnostic testing will increase.
Can PSY testing be done by the Virginia NBS state laboratory?	• Requires high end mass spectrometer. • Projections of 10-20 infants needing 2nd tier PSY may be more cost effective to outsource testing. • The state laboratory will determine optimal processes with existing testing methodologies, equipment, and algorithms.
What is goal for this screening program? Is it to identify EIKD or all forms of Krabbe?	• Krabbe is not currently on RUSP, no specific guidelines for targets- the workgroup recommendation would inform targeted screening goal. • Although NBS screening has been shown to identify EIKD, it can also identify small subset of additional at risk newborns for LOKD. • Newborn screening is a public health initiative and not a clinical tool for diagnosing.

	• NBS should be used as public health platform to use with evidence that has undergone very extensive and aggressive peer review. • The parents stated that the goal would be to identify EIKD.
Depending on how screening cut-offs are set, possibility to pick up false positives, LOKD, and EIKD.	• NY NBS mentioned challenges with PSY cutoff levels. • Need to target the specified affected group clearly. • Referenced KY success with PSY and NBS (zero false positives). • Genetics has concerns of following possible LOKD and counseling parents with false positives- referenced experience with the Lysosomal Storage Disorders, Pompe and MPSI and high false positives.
Is prenatal testing a possible better avenue for screening for Krabbe Disease?	• If identified through prenatal testing as carrier status, amniocentesis could inform if baby is at risk and refer to specialist at 20 weeks. • Concerns that there is not standard, universal testing. Providers are not informed and not offering to parents. • Newborn screening is only universal public health screening program at this time. • Knowledge of risk may facilitate appropriate future medical care planning and reproductive decisions for families. • The parents of the workgroup testified that NBS for Krabbe was never offered or discussed by their health care providers.
Potential for earlier diagnosis of Krabbe Disease for approximately 1 family per year in the state of Virginia	• The addition of PSY to Krabbe Disease NBS testing algorithms reduces previous concerns of high false positives. • Recommended screening algorithms are complex and requires multi-tier testing. • This is a very rare condition. Based on the most recent NY data, it is less common than any of the other conditions currently on the Virginia NBS panel. Incidence is actually lower than previously estimated (1:250,000). Virginia averages approximately 100,000 births annually.
Identifying infants at risk of developing Krabbe and offering a modestly effective therapy (HSCT) before symptom onset.	• Krabbe Disease is a complex disorder with variable ages of onset. There is no established correlation between enzyme level and age of onset or severity of the disorder. The methodology used for newborn screening will also identify individuals affected with late-onset forms of the disease, even with the recommended PSY stratification. There is no genotype/phenotype correlation, so even an individual with two mutations may never become symptomatic. There is no way to predict when they might develop disease. • The current treatment of HSCT transplant for an identified EIKD baby is not considered to be a cure. It can halt the progression of the disease; however, it will not reverse existing damage. It is

	possible that future gene therapy treatment could further improve outcomes. • There is no pediatric HSCT transplant center in Virginia. Two disorders currently on Virginia's newborn screening panel require HSCT and the genetic centers have experienced a delay in treatment from seeking care outside of Virginia. This delay is even more significant with state insurance and signifies inequality and barriers for access to care. • Myelination begins in a fetus at approximately 26 weeks of life. It is possible that severe forms of EIKD could be symptomatic at birth. It was advised by the Krabbe experts that HSCT transplant would not be recommended if a baby was symptomatic. • Screening methodology could possibly increase recommended turnaround time of reporting results for other disorders on Virginia's NBS panel. • DNA testing will be required to follow-up on initial positive screens. Many carriers of Krabbe Disease are likely to be identified that will then necessitate referrals for genetic counseling. • Insufficient understanding of the genotype-phenotype correlation in this disorder o This results in a poor predictive value of diagnostic confirmatory testing. o As a result, a much larger number of potentially healthy babies with borderline results will be 'medicalized' and will require long-term medical follow-up.
Parent Perspectives	• Normal pregnancy, baby born healthy and told 6 months later that the baby will die a slow, painful death. • Previous meeting and discussion focused on no absolute "cure." • No absolute "cure" for cancer patients but still treated. • Parents should be able to make the choice for treatment. • Cost should not be a factor for a child's life. • Concerned about more affected babies being born with no potential for positive outcome due to late diagnosis.

I. Summary of 2020 VDH Krabbe Disease Workgroup Recommendations

At the third and final Krabbe Disease workgroup session on September 3, 2020, a public comment period was held. Six individuals spoke in favor of adding Krabbe Disease to Virginia's newborn screening panel and shared personal stories describing how their lives have been impacted by Krabbe Disease. They stated that they would have wanted a choice if they had known about the diagnosis early enough to begin treatment for their babies.

Dr. Jamie Fraser made a motion to vote on a recommendation to add Krabbe Disease to Virginia's newborn screening panel. The motion was followed by discussion that addressed clarification regarding

whether the motion was for EIKD or all forms of Krabbe Disease, concerns about costs and impact to hospitals, and the fact that Krabbe Disease is not currently on the ACHDNC RUSP. Dr. Fraser rescinded her motion to allow opportunity for additional discussion.

Kasey Feldt made a motion for Krabbe Disease to be added to Virginia's newborn screening panel. Lana Grujicic seconded the motion. No additional discussion on the motion occurred. A formal voice vote occurred with the following votes recorded (5-Yes, 4-No, 2-Abstain, and 1-Absent):

Yes (5)
Kim Pekin, CPM
Jana Monaco, Advocate, Parent
Dragan Grujicic, Parent
Lana Grujicic, Parent
Kasey Feldt, Parent

No (4)
Dr. Jamie Fraser, CNMC, Genetics
Dr. Hind Al Saif, VCU, Genetics
Jennifer Lent, Genetic Counselor, VCU, Genetics
Brianna Murray, Genetic Counselor, CHKD, Genetics

Abstain (2)
Jullie Rhee, NP, CNMC, Neurology
Abraham Segres, VHHA

Absent (1)
Dr. Bill Wilson, UVA, Genetics

Note: VDH and DCLS staff abstained from voting.

Summary of the Newborn Screening Advisory Committee Meeting and Recommendation

The Newborn Screening Advisory Committee (NBS AC) was created to consult and advise the Virginia Newborn Screening Program (VNSP) and the Health Commissioner on the screening of newborns in the Commonwealth of Virginia for heritable disorders in order to reduce morbidity and mortality in newborns and children who have, or are at risk for, these heritable disorders. Members of the NBS AC include stakeholder representatives throughout the Commonwealth who work in the field of newborn screening as well as parent representatives. Members are expected to make informed decisions and to ensure that any recommendations developed by the Advisory Committee shall be representative of the stakeholder organizations the member represents. VDH and DCLS staff serve as staff and technical consultants to the advisory committee.

Current NBS AC Membership list as of November 12, 2020:

UVA	Dr. William Wilson (Chair)
VCU	Dr. Hind Al Saif
CHKD/EVMS	Dr. Samantha Vergano
CNMC	Dr. Christine Grant
INOVA Health Systems	Dr. Marta Biderman Waberski
DoD facilities	Dr. Stephanie Smith
MOD	*Vacant*
VHHA	Abraham Segres
Virginia AAP	Dr. Jane Die
Virginia ACOG	Dr. Christian Chisholm
Community Pediatrician	Dr. Richard Bennett
Community Pediatrician	Dr. Sylvia Lee
Neonatologist	Dr. Brooke Vergales
RN – Well baby Nursery	Karen Shirley
RN – NICU	Lisa Shaver
CPM	Kim Pekin
Virginia American College of Nurse Midwives	Katie Page
Certified Genetic Counselor	Rachel Gannaway
Registered Dietician	Eileen Coffman
Parent Advocate	Jana Monaco
Parent Advocate	Julie Murphy
DCLS Staff	Emily Hopkins
VDH Staff	Christen Crews

The NBS AC convened on Thursday, November 12, 2020 for its scheduled bi-annual meeting. A quorum of the NBS AC board was met with 19 of the 21 board members present. A few weeks prior to the

meeting, all NBS AC board members who did not participate in the Krabbe disease workgroup sessions were provided access to the VDH 2020 Krabbe Disease Review website (https://covgov.sharepoint.com/sites/VDH-KrabbeReview2020-External).

A public comment period was held at the start of the meeting. Nine individuals spoke during the public comment period, providing testimony in support of adding Krabbe Disease to Virginia's newborn screening panel. The speakers included parents, advocacy groups, a pediatrician, and a NBS scientist. The speakers advised that the lives of children who receive treatment for EIKD are vastly different than those who are not diagnosed in time. Newborn screening has improved significantly since NY started screening in 2006. Parents provided testimony of their experience with the diagnostic odyssey and grief upon finding that treatment cannot occur once symptomatic. Their goal is to add Krabbe Disease to Virginia's newborn screening panel to save future children in Virginia and to give parents a choice for treatment.

Delegate Jason Miyares (Patron of HB97) addressed the NBS AC and strongly encouraged committee members to vote to recommend the addition of Krabbe Disease to the Virginia newborn screening panel. Christen Crews provided a presentation to the NBS AC, reviewing the series of Krabbe Disease workgroup sessions. Presentation content included an overview of the presentations provided by the Krabbe Disease experts; data and experiences from other NBS programs; concerns and discussions of the workgroup members; parent perspectives; potential fiscal impact; and the final motion of the workgroup to recommend Krabbe Disease to be added to the Virginia Newborn Screening Panel (vote of 5-Yes, 4- No, 2- Abstain, and 1- Absent).

Recommended Universal Screening Panel

The floor was opened to the NBS AC members for discussion of the workgroup review and Krabbe Disease. Many concerns were expressed about the fact that Krabbe Disease was not currently on the RUSP. Several NBS AC members stated that they would have less concern with recommending the addition of Krabbe Disease to Virginia's newborn screening panel if it was on the RUSP. The NBS AC members were informed that the Krabbe NBS Council has formed a workgroup and is in the process of reapplying to the ACHDNC for reconsideration of adding Krabbe Disease to the RUSP.

Fiscal Impact

Advisory committee members discussed the fiscal impact of adding Krabbe Disease to Virginia's screening panel, as these costs are passed to the hospitals, out-of-hospital care providers, or self-paying parents through a fee increase. VNSP program staff advised that the projected cost analysis includes the cost for purchasing equipment (i.e. mass spectrometry), as the VNSP is currently screening for two lysosomal storage disorders (Pompe and MPSI) on a different platform that is not compatible for Krabbe testing. These two disorders would need to transition to the new platform for the laboratory workflow to include screening for Krabbe Disease. The second tier and third tier cost estimates for PSY and molecular testing (gene sequencing) were derived from estimates of projected case numbers based on information presented by Krabbe Disease experts in the workgroup sessions. Other costs factored into

the estimate included laboratory staffing, infrastructure (laboratory information management system), and staffing for the VDH follow-up program.

Follow-Up for Intermediate/Borderline Cases

There was reference to the work that the NY NBS program and Krabbe Disease experts have done to overcome barriers previously mentioned in the 2015 review. A concern regarding follow-up for the indeterminate/borderline group (PSY of 2-10 with proposed stratification from workgroup) was dicussed. The previous follow-up algorithm was invasive and highly medicalized for those who were not clearly negative or positive. Due to the addition of PSY to the NBS algorithm and the NY NBS experience, the new recommended follow-up guidelines have resulted in an estimated 88% reduction in follow-up diagnostic testing for intermediate cases in the first two years from the time of initial diagnosis (*Figure 4*).

Previous Guidelines:

47 patients	Total pts	LP	MRI	NCS	BAER
High risk	36	216	216	216	216
Mod risk	11	22	22	22	22

88% reduction in diagnostic testing in the first 2 years

New Guidelines:

47 patients	Total pts	LP	MRI	NCS	BAER
High LOKD	8	0	48	40	0
Low LOKD	15	0	15	15	0
Unaffected	24	0	0	0	0

Figure 4: Provided by Dr. Robert Stone, 2020 Hunter's Hope Symposium

Although the previous concern regarding the high false positive (FP) rate has been reduced with the addition of PSY testing to the recommended Krabbe NBS algorithm (as evidenced by Kentucky having a zero FP rate), data was presented from the NY NBS program that 45 positives were referred to genetics with only about 20 demonstrating elevated PSY levels. These babies will need to have additional testing and possibly long term follow-up while waiting for clinical manifestations of Krabbe Disease to develop or to be diagnostically cleared. This data was compared to the data for the two LSDs currently on Virginia's newborn screening panel that require a wait time of several weeks for second tier results, as well as a large number of infants that are considered to be borderline (variants of uncertain significance or possible late-onset) and needing to be followed on a long-term basis by the genetics centers.

Treatment and Insurance Barriers

The workgroup discussions and data presented only provided evidence of one EIKD (KY) case that was exclusively identified through NBS, without any family history of a sibling or prenatal diagnosis. Several of the NBS AC board members had concerns with the timeline of identifying a baby with NBS as the minimum turnaround time for results with second tier PSY testing is estimated at eight days, and getting the infant transplanted prior to 30 days of life. Additional planning and preparation can be made if family history or prenatal diagnosis exists to decrease delays in treatment. Additionally, donor selection can be lengthy and may potentially result in missing the window of time for treatment.

Virginia does not have a pediatric HSCT transplant center at this time. Other states that are currently screening for Krabbe Disease have the treatment available. The NBS AC board members shared several examples of prior experiences with referrals to transplant centers outside of Virginia, including a recent referral to Duke for a severe MPSI case. In these situations, it has taken months for the baby to receive a transplant, and additional equity issues exist for the Virginia Medicaid population with access to treatment. This is not a novel issue for Krabbe Disease, as it has been a challenge that the genetic specialists have been battling with insurance companies for years and a huge barrier remains for receiving timely treatment. The NBS AC members expressed significant concerns about insurance barriers causing delays given the narrow treatment window for Krabbe Disease. A genetic specialist may have to communicate with a parent that NBS has detected a disorder but treatment is not an option because of symptom onset. One committee member stated that this situation goes against the fundamental principles of newborn screening.

Dr. Brooke Vergales made a motion to approve the addition of Krabbe Disease to Virginia's newborn screening panel. Dr. Sophia Lee seconded the motion. No additional discussion on the motion occurred. A formal voice vote occurred with the following votes recorded (9-No, 6- Yes, 4- Abstain, and 2- Absent):

No (9)
Abraham Segres, VHHA
Dr. Christina Grant, CNMC
Dr. Jane Die, Virginia Chapter AAP
Dr. Hind Al Saif, VCU
Dr. Samantha Vergano, EVMS/CHKD
Dr. Brooke Vergales, Neonatologist, UVA
Eileen Coffman, Registered Dietitian
Dr. Marta Biderman Waberski, INOVA
Dr. Bill Wilson, UVA, Chair

Yes (6)
Lisa Shaver, Children's Hospital of Richmond at VCU
Rachel Gannaway, Genetic Counselor, VCU
Dr. Richard Bennett, Community Pediatrician
Dr. Sylvia Lee, Community Pediatrician

Jana Monaco, NORD, Parent
Kim Pekin, CPM

Abstain (4)
Julie Murphy, Parent
Karen Shirley, HCA-Va, Chippenham Hospital
Dr. Stephanie Smith, DOD, Portsmouth Naval Medical Center
Katie Page, American College of Nurse Midwives

Absent (2)
Dr. Christian Chisholm, UVA, ACOG
Vacant, MOD

The NBS AC agreed that the VNSP should remain consistent with federal recommendations and that the data does not support the use of newborn screening for Krabbe Disease at this time. Specifically the discussions of the NBS AC board members demonstrated:

- Krabbe Disease is not one of the disorders on the RUSP. Disorders on the RUSP are chosen based on evidence that supports the potential net benefit of screening, the ability of states to screen for the disorder, and the availability of effective treatments. Krabbe Disease was reviewed for consideration to be added to the RUSP in 2009 and not approved;
- The lack of data on the number of EIKD cases exclusively identified through NBS without any family history or prenatal diagnosis;
- The inability for identified infants to receive care within Virginia due to the lack of an available pediatric transplant center. Concerns of receiving treatment within a narrow window with documented cases of delays in receiving care outside of the state and inequality for the Virginia Medicaid population;
- The potential for a high rate of intermediate or borderline results (PSY of 2-10) and lack of genotype/phenotype correlation will lead to significant psychological distress and a medical odyssey for families in attempting to confirm or refute the diagnosis.

The Virginia NBS AC would reconsider the addition of Krabbe Disease to Virginia's NBS AC panel in the future if it is added to the ACHDNC's RUSP for core newborn screening disorders.

RECOMMENDATION: The NBS AC made the formal recommendation that Krabbe Disease should not be added to Virginia's Newborn Screening panel at this time.

References

1. Allewelt H, Taskindoust M, Troy J, et al. Long-Term Functional Outcomes after Hematopoietic Stem Cell Transplant for Early Infantile Krabbe Disease. Biol Blood Marrow Transplant. 2018;24(11):2233-2238. doi:10.1016/j.bbmt.2018.06.020

2. Bascou N, DeRenzo A, Poe MD, Escolar ML. A prospective natural history study of Krabbe disease in a patient cohort with onset between 6 months and 3 years of life. Orphanet J Rare Dis. 2018;13(1):126. Published 2018 Aug 9. doi:10.1186/s13023-018-0872-9

3. Beltran-Quintero ML, Bascou NA, Poe MD, et al. Early progression of Krabbe disease in patients with symptom onset between 0 and 5 months. Orphanet J Rare Dis. 2019;14(1):46. Published 2019 Feb 18. doi:10.1186/s13023-019-1018-4

4. Blackwell, K.; Gelb, M.H.; Grantham, A.; Spencer, N.; Webb, C.; West, T. Family Attitudes Regarding Newborn Screening for Krabbe Disease: Results from a Survey of Leukodystrophy Registries. Int. J. Neonatal Screen. 2020, 6, 66.

5. Dees, R.; Kwon, J. The Ethics of Krabbe Newborn Screening, Public Health Ethics, Volume 6, Issue 1, April 2013, Pages 114–128, https://doi.org/10.1093/phe/phs033

6. Dimmock DP. Should states adopt newborn screening for early infantile Krabbe disease? Genet Med. 2016;18(3):217-220. doi:10.1038/gim.2016.6

7. Duffner PK, Caggana M, Orsini JJ, et al. Newborn screening for Krabbe disease: the New York State model. Pediatr Neurol. 2009;40(4):245-255. doi:10.1016/j.pediatrneurol.2008.11.010

8. Ehmann, P. and Lantos, J.D. (2019), Ethical issues with testing and treatment for Krabbe disease. Dev Med Child Neurol, 61: 1358-1361. doi:10.1111/dmcn.14258

9. Escolar ML, Kiely BT, Shawgo E, et al. Psychosine, a marker of Krabbe phenotype and treatment effect. Mol Genet Metab. 2017;121(3):271-278. doi:10.1016/j.ymgme.2017.05.015

10. Escolar ML, Poe MD, Provenzale JM, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med. 2005;352(20):2069-2081. doi:10.1056/NEJMoa042604

11. Guenzel AJ, Turgeon CT, Nickander KK, et al. The critical role of psychosine in screening, diagnosis, and monitoring of Krabbe disease. Genet Med. 2020;22(6):1108-1118. doi:10.1038/s41436-020-0764-y

12. Ida H, Rennert OM, Watabe K, Eto Y, Maekawa K. Pathological and biochemical studies of fetal Krabbe disease. Brain Dev. 1994;16(6):480-484. doi:10.1016/0387-7604(94)90013-2

13. Kemper AR, Knapp AA, Green NS, Comeau AM, Metterville DR, Perrin JM. Weighing the evidence for newborn screening for early-infantile Krabbe disease. Genet Med. 2010;12(9):539-543. doi:10.1097/GIM.0b013e3181e85721

14. Kurtzberg J, Buntz S, Gentry T, et al. Preclinical characterization of DUOC-01, a cell therapy product derived from banked umbilical cord blood for use as an adjuvant to umbilical cord blood transplantation for treatment of inherited metabolic diseases. Cytotherapy. 2015;17(6):803-815. doi:10.1016/j.jcyt.2015.02.006

15. Kwon JM, Matern D, Kurtzberg J, et al. Consensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. Orphanet J Rare Dis. 2018;13(1):30. Published 2018 Feb 1. doi:10.1186/s13023-018-0766-x

16. Lantos JD. Dangerous and expensive screening and treatment for rare childhood diseases: the case of Krabbe disease. Dev Disabil Res Rev. 2011;17(1):15-18. doi:10.1002/ddrr.133

17. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S. Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015;39(3):206-216. doi:10.1053/j.semperi.2015.03.005

18. Minter Baerg MM, Stoway SD, Hart J, et al. Precision newborn screening for lysosomal disorders. Genet Med. 2018;20(8):847-854. doi:10.1038/gim.2017.194

19. Orsini JJ, Escolar ML, Wasserstein MP, et al. Krabbe Disease. 2000 Jun 19 [Updated 2018 Oct 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1238/

20. Orsini JJ, Saavedra-Matiz CA, Gelb MH, Caggana M. Newborn screening for Krabbe's disease. J Neurosci Res. 2016;94(11):1063-1075. doi:10.1002/jnr.23781

21. Saha A, Buntz S, Scotland P, Xu L, Noeldner P, Patel S, et al. A cord blood monocyte-derived cell therapy product accelerates brain remyelination. JCI Insight. 2016;1:e86667.

22. Saha A, Patel S, Xu L, Scotland P, Schwartzman J, Filiano AJ, et al. (2019) Human umbilical cord blood monocytes, but not adult blood monocytes, rescue brain cells from hypoxic-ischemic injury: Mechanistic and therapeutic implications. PLoS ONE 14(9): e0218906. https://doi.org/10.1371/journal.pone.0218906

23. Steiner, Robert. (2009). Newborn Screening for Krabbe Disease: the New York State Model. Pediatric neurology. 40. 253-5. 10.1016/j.pediatrneurol.2009.01.001

24. Steiner RD. Commentary on: "Newborn screening for Krabbe Disease: the New York state model" and "the long-term outcomes of presymptomatic infants transplanted for Krabbe disease. A report of the workshop held on July 11 and 12, 2008, Holiday Valley, New York". Genet Med. 2009;11(6):411-413. doi:10.1097/GIM.0b013e3181a7e910

25. Wasserstein MP, Andriola M, Arnold G, et al. Clinical outcomes of children with abnormal newborn screening results for Krabbe disease in New York State. Genet Med. 2016;18(12):1235-1243. doi:10.1038/gim.2016.35

26. Wright MD, Poe MD, DeRenzo A, Haldal S, Escolar ML. Developmental outcomes of cord blood transplantation for Krabbe disease: A 15-year study. Neurology. 2017;89(13):1365-1372. doi:10.1212/WNL.0000000000004418