The Virginia Genetics 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
May 5, 2015

Background to Commissioner's Charge

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. The proposed language was to be added to the Code of Virginia, specifically § 32.1-65.

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" (SACHDNC). 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 32 disorders that are included in the RUSP.

Section 12 VACS-71-30 also outlines the process by which disorders are added to Virginia's panel. This process requires any disorders being considered for addition to the VA core panel to be reviewed by the Virginia Genetics Advisory Committee (VAGAC) resulting in a formal report to the Board of Health through the State Health Commissioner. This process was made known to both sponsors during their respective subcommittee meetings. As a result, in a letter dated January 26, 2015, Senator Edwards requested that the Commissioner initiate a review of Krabbe Disease and make formal recommendations for or against addition to Virginia's newborn screening panel.

In response to Senator Edwards, the Commissioner of Health, in a letter dated February 3, 2015, charged the VAGAC to review the SACHDNC's evidence-based review of Krabbe Disease from 2009 and to make recommendations to the Board of Health on "…the potential costs, risks, and benefits of adding Krabbe Disease to the Virginia Newborn Screening Panel."

Krabbe Disease

In the United States, it is estimated that Krabbe Disease affects about 1 in 100,000 individuals (1). Krabbe Disease is an inherited, degenerative disorder of the central and peripheral nervous systems and can be classified as both a leukodystrophy and as 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 age six months (2) and is categorized as Early Infantile Krabbe Disease (EIKD). Other categories of Krabbe Disease variants occur as late infantile, juvenile/adolescent or adult stages of life and may progress more slowly (1,3). 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 age two (2,3).

Screening and diagnosing EIKD can be complex and challenging due to the large number of possible *GALC* gene mutations and unpredictability of disease course. (2,3). There is no cure for Krabbe Disease. Generally, treatment for the disorder is symptomatic and supportive. Dietary enzymatic treatment has not been effective in either reversing the symptoms or halting disease progression and is therefore not considered an efficacious treatment option (3). 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.

Krabbe Disease Workgroup

A workgroup of the VAGAC was formed in response to the Commissioner's charge. The workgroup members represented the Virginia Department of Health (VDH), the Division of Consolidated Laboratory Services (DCLS), medical experts of multiple professions in the field of Krabbe Disease from all major medical and higher education institutions within the Commonwealth and a parent advocate. All workgroup participants agreed to the meeting being recorded in order to enhance the authenticity of meeting minutes.

The following workgroup members convened on May 5, 2015 at DCLS to start its initial review:

- Jennifer Macdonald, Public Health Nurse Manager, Newborn Screening Program, VDH
- Kim Turner, Newborn Screening Group Manager, DCLS
- Willie Andrews, Director of Laboratory Operations, DCLS
- Wendy Mallory, Follow-up Nurse, VDH
- Cornelia Deagle, Director, Division of Child and Family Health, VDH
- Dev Nair, Director, Division of Policy and Evaluation, VDH
- Rhonda West, Scientist, DCLS
- Richard Haughton, Principal Scientist, DCLS
- Jean Stankavich, Senior Scientist, DCLS
- Jacob Sams, Children's National Medical Center
- Nicholas Ahmew, MD Genetics and Metabolism, Children's National Medical Center
- Marshall Summar, MD Division Chief, Genetics and Metabolism, Children's National Medical Center
- Sarah Viall, PNP, Genetics and Metabolism, Children's National Medical Center
- Elizabeth Chisholm, Genetic Counselor, Genetics, Children's Hospital of the Kings Daughters
- Katherine Langley, Genetic Counselor, Genetics, Children's Hospital of the Kings Daughters
- William G. Wilson, MD, Genetics and Metabolism, University of Virginia
- Rachel Gannaway, Genetic Counselor, Virginia Commonwealth University
- Jana Monaco, Parent Advocate on Virginia Genetic Advisory Committee and member of the Organic Acidemia Association (OAA) and National Organization for Rare Disorders (NORD)

Workgroup Review

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

SACHDNC received a nomination of Krabbe Disease, specifically EIKD for inclusion in the Committee's RUSP for state newborn screening programs in 2010. 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 (www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/nominatecondition/reviews/krabbedisease.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) not definitive. 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 SACHDNC determined that it would not add Krabbe Disease to the RUSP. The SACHDNC identified the following evidence gaps in their letter to the Secretary (4):

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.*

Due to their state legislative mandates, New York and Missouri are the only states currently screening for Krabbe Disease. Other states, such as Illinois, New Mexico, Pennsylvania and Kentucky have passed legislation adding Krabbe Disease to their panels but have not yet implemented screening.

B. Scientific Review of Krabbe Disease

The VAGAC workgroup reviewed the scientific literature published after the release of the 2009 SACHDNC report and data generously provided by the New York Newborn Screening Laboratory. The New York Newborn Screening Program has been screening its infants for Krabbe Disease since 2006 and has also been screening Missouri's newborn specimens since 2012. As of April 2015, NY screened over 2,333,587 specimens for Krabbe Disease. Specimens are initially screened for GALC activity and if warranted, second tier DNA testing is conducted. This second tier screening is aimed at reducing the number of false positive results. See Figure 1 in the Appendix for detailed description of New York's screening algorithm.

Results are categorized based on GALC activity and number of mutations found as follows:

1) No Risk
2) Moderate Risk
3) High Risk

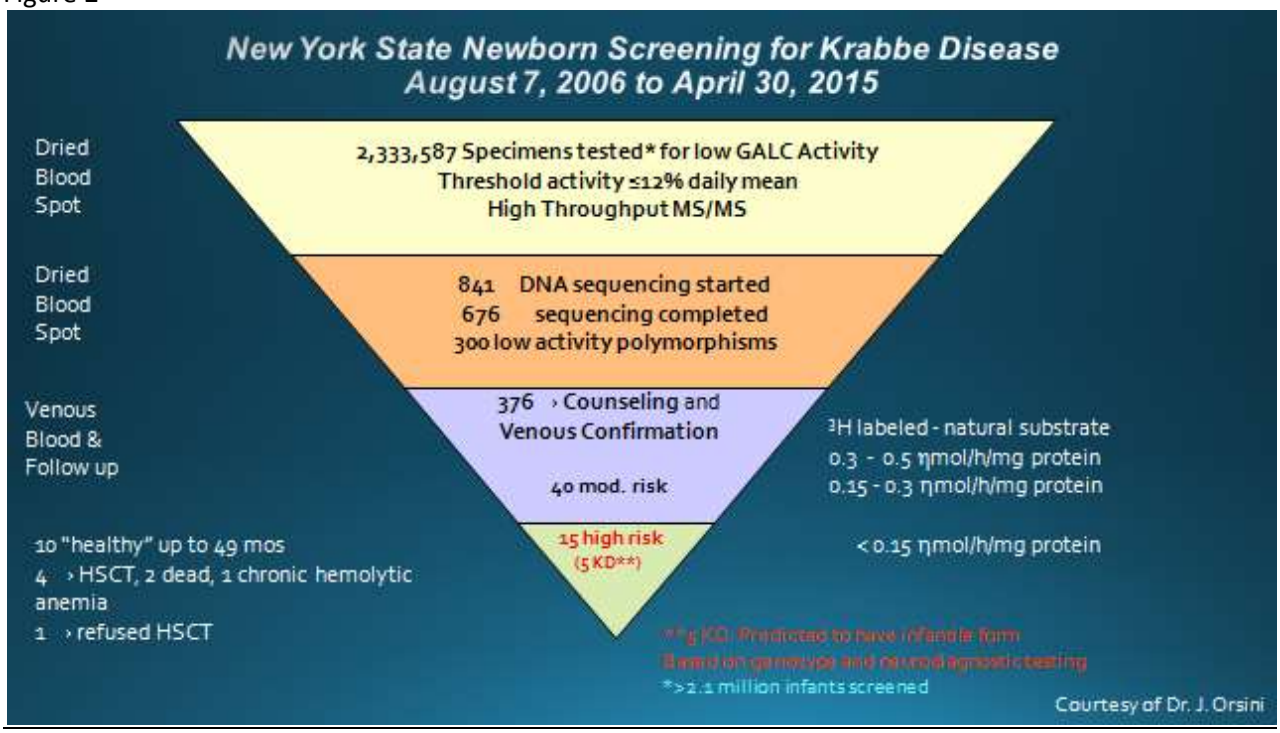
Figure 2 shows the results of over two million specimens that have been screened as of April 2015. Approximately 376 infants were referred for genetic counseling and further diagnostic workup. Fifteen (15) infants were found to be high risk, 5 of which were predicted to have EIDK. Ten infants, though deemed "healthy", continue to have the diagnostics done at different intervals to assess clinical status and need of possible HSCT. The economical and psycho-social impact of this has not been studied. Four infants have received HSCT, three of which passed away from complications. One infant experienced chronic hemolytic anemia post transplant and one was transplanted late and requires continuous medical care. Genetic Counseling also plays a major role in New York's program, especially for families who have been identified as carriers of the disease.

Prior to New York's screening program, the incidence of Krabbe Disease was thought to be 1:100,000 (2). Based on the information shared by the New York Newborn Screening Program, the incidence has now been ascertained to be 1:420,000.

The low positive predictive value (PPV) of ~9% has not changed significantly over the years New York has been screening infants for Krabbe Disease. This means that approximately 9% of infants who *screened positive* actually have the disease. The PPV may increase if diagnosis of Krabbe disease is made in infants who screen positive (3).

Based on New York's data, the workgroup ascertained that Virginia would expect approximately 42 infants requiring DNA sequencing and approximately 20 infants referred for further diagnostic testing annually.

Figure 2



C. Infrastructure Needs in Virginia

The process for setting up Krabbe Disease screening in Virginia would be a multiyear project. The workgroup identified the following infrastructure needed by VNSP to screen for Krabbe Disease:

1. Additional equipment to support the screening methodology:
    a. 3 Mass Spectrometers
    b. 2 Liquid Handlers
    c. 2 Centrifuges
    d. Nitrogen Generation Equipment
    e. Reagents (an annual cost)
    f. Equipment Maintenance support (an annual cost)

2. Additional space and environmental modifications at DCLS to provide second tier molecular screening.

3. Four additional programmatic FTEs at DCLS (3) and VDH (1) to conduct project planning, set-up and validation of chosen screening methodology, planning and developing education, creating follow-up algorithms and reporting documents and actual screening.

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

5. Incorporation of new education module specific to Krabbe Disease screening into current educational website (located at newbornscreeningeducation.org) and continued maintenance of this 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.

D. 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 $78 per card. This fee was last raised on January 1, 2014 due to the anticipated addition of Severe Combine Immune Deficiency (SCID). 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 $2,416,000.00, and that subsequent years would require an estimated $573,000.00 annually. It should be noted that these costs would increase significantly if molecular sequencing was implemented as a part of the testing algorithm.\

A Fiscal Impact Statement (FIS) was submitted to the Department of Planning and Budget (DPB) during the 2015 General Assembly in response to HB1420/SB835. The workgroup reviewed this estimate and identified additional information and concerns.

1. It estimated that a $10-20 fee increase would need to occur to cover the potential cost of adding Krabbe Disease to the newborn screening panel. This increase would support the infrastructure needs identified by the group.

2. The workgroup also noted that the estimate provided by the Virginia's Department of Medical Assistance Services (DMAS) on the FIS to DPB was significantly underestimated and that research would need to be performed to provide a more accurate cost for the potential diagnostic and treatment of those infants who not only may be diagnosed with Krabbe Disease, but those infants that will fall into a risk category that will constitute continued diagnostic assessment.

Benefits and Risks of Screening for Krabbe Disease

After the review of the most recent published literature regarding Krabbe Disease and data from the New York Newborn Screening Program, the workgroup provided the benefits and risks to screening for Krabbe Disease in Virginia, as seen from their unique perspectives. These comments were made in person at the workgroup meeting and then again, in writing, following the meeting. The identified benefits and risks are listed in Table 1.

Table 1

IDENTIFIED BENEFITS TO SCREENING FOR KRABBE DISEASE RELATED TO…	***IDENTIFIED RISKS TO SCREENING FOR KRABBE DISEASE RELATED TO…***
DATA	***DATA***
Better understanding of the natural history of Krabbe	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 & thoughtfully reviewed at the national level and the SACHDNC has not recommended that Krabbe Disease be added to the RUSP.
	Gaps in evidence from 2009 SACHDNC committee report still exist.
INFRASTRUCTURE	***INFRASTRUCTURE***
By adding Krabbe Disease to the Virginia newborn screening panel, DCLS testing would need to be modified. Those modifications might put Virginia in position to add other lysosomal storage diseases in the future as testing technology, follow-up testing and as treatment improves.	Adding Krabbe disease to the Virginia panel would add significant cost to the lab and to follow-up, and this cost would either be passed on to the hospitals and families with newborn infants or would need to be budgeted by the legislature.
	Cost benefit ratio is not where it should be with screening costs.
	Language in HB1420/SB835 is very vague and could lead to the addition of other lysosomal storage disorders to the newborn screening panel. Most of these disorders have the associated risks as listed above.
IDENTIFICATION & DIAGNOSIS	***IDENTIFICATION & DIAGNOSIS***
Potential for earlier diagnosis of Krabbe disease for approximately 1-2 families per year in the state of Virginia	There is a possibility of a high false positive rate in screening. The screening and follow-up testing have significant problems, including the difficulty in actually identifying a patient with infantile onset Krabbe disease and not one of the other variants,

	some of whom may have no symptoms. Positive predictive value (PPV) of screening and testing is low enough that the resulting uncertainty carries a very high care burden with an adverse risk/benefit ratio
Knowledge of risk may facilitate appropriate future medical care planning and reproductive decisions for families	This is a very rare condition. Based on 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.
May identify one infant every 2-4 years in Virginia with infantile Krabbe disease and for whom transplant might be initiated.	Screening algorithm in place in NY is complex and requires multi tier testing.
Identifying infants at risk of developing Krabbe and offering a modestly effective therapy (HSCT) either before or at the onset of symptoms	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. 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.
Reducing or eliminating the 'diagnostic odyssey' for families with children affected with Krabbe	Screening methodology not FDA approved
	Screening methodology would increase recommended turnaround time of reporting results.
	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.
	FOLLOW-UP AND TREATMENT
	The evidence that the current therapy for patients with infantile Krabbe Disease will make a significant long-term difference for these children is weak. The therapy for infantile Krabbe Disease is invasive and high risk. Mis-identifying a child as needing therapy could result in significant morbidity and mortality. Therapy is unproven clearly in affected cases and "borderline" cases.
	Current clinical theory of presymptomatic bone marrow transplant would lead to exposure of a number of unaffected or mildly affected patients to a dangerous and impactful procedure.

	The clinical and psychological burden of monitoring all patients with an abnormal screen prospectively will need to be considered.
	Treatment for Krabbe with hematopoietic stem cell transplant (HSCT) is not 100% curative, and has a high mortality rate. Identification of the disease in the newborn period is therefore not likely to significantly change the outcome in these children. HSCT can only be used in the infantile form; there is currently no treatment for the adult onset form. There is a real risk for children, who may never develop symptoms, to unnecessarily undergo HSCT due to parental concern as a result of the NBS. This scenario would certainly lead to direct patient harm, which is contrary to the purpose of the VDH NBS.
	There is likely to be a high rate of false positive screens; this, in addition to the necessary confirmatory testing, could potentially lead to significant psychosocial impact to these families. In this situation, the family's autonomy is at risk, and directly affects the principle of beneficence and non-maleficence.
	Positive screening likely to lead to a medical odyssey in attempting to confirm or refute the diagnosis
	May subject unaffected children to invasive and dangerous medical procedures in the work-up to diagnosis alone (MRIs requiring sedation, nerve conduction studies etc.) not to mention if deciding to treat
	Even in truly affected children, treatment (HSCT) is not necessarily effective and most certainly dangerous.
	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 individuals will be 'medicalized' and will require long-term medical follow-up. o Some of these families may be offered HSCT, and may proceed with this risky procedure despite not having the disorder.

	The best available therapy at this time is Hematopoietic Stem Cell Transplant (HSCT), which is high-risk, yet not a complete cure, and of only modest clinical benefit.
	Krabbe NBS at this time will only create a much larger group of families who will need to endure going from one doctor's appointment to the next without obtaining a diagnosis for their child.

F. Summary of VAGAC Workgroup Recommendations

The workgroup was formally polled and voted unanimously against the addition of Krabbe Disease to the Virginia Newborn Screening Panel at this time (0-Yeas, 9 Nays). Note: VDH and DCLS staff abstained from voting.

The workgroup felt strongly that the VNSP should remain consistent with federal recommendations and that the data and unproven clinical options do not support the use of newborn screening for Krabbe Disease at this time. Specifically the review demonstrated:

- There is a lack of clear consensus on what exactly constitutes EIKD;
- The current screening for Krabbe Disease is complex, expensive and has a low 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;
- The high rate of false positive screening results will lead to a significant psychological distress and a medical odyssey in attempting to confirm or refute the diagnosis.

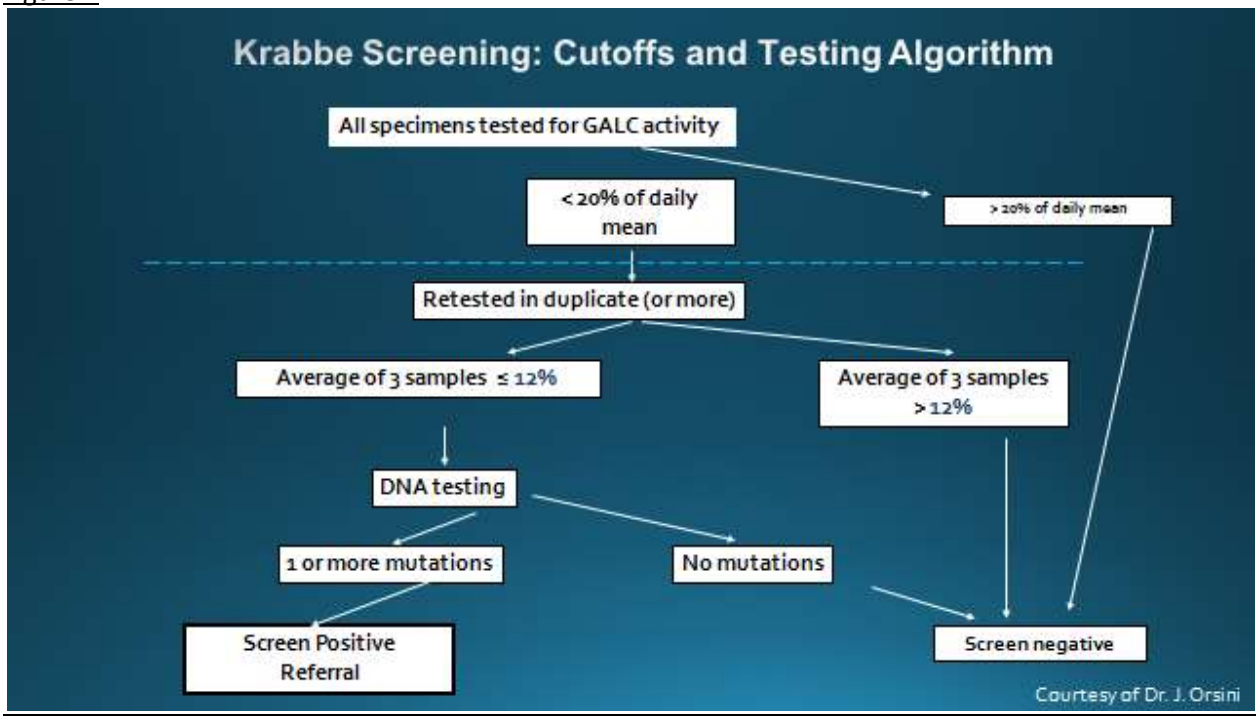
The workgroup does acknowledge the importance of family support for those infants who are undergoing diagnostic testing and treatment of Krabbe Disease as well as need to educate the Commonwealth's medical providers on this devastating disease.

The following formal recommendations were made by the workgroup:

1) Based on current evidence Krabbe Disease should not be added to Virginia's Newborn Screening panel at this time.
2) A robust educational campaign for clinicians would be a better application of the Commonwealth's resources. The goal would be to improve the "diagnostic odyssey" that families go through to arrive at a Krabbe Disease diagnosis so that these patients may be identified sooner. Acquiring funding for the development of such educational materials for clinicians was not explored during the workgroup meeting and would have to be determined by the legislature.
3) This report should be made transparent and easily accessible to families to further the understanding of the position taken at this time and to dispel beliefs that the decision was strictly cost-driven.
4) Relevant advocacy groups would benefit from communication on what evidence is needed to improve the possibility of adding Krabbe Disease to the Recommended Uniform Screening Panel (RUSP) in the future.

Appendix

Figure 1



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