

Expansion of the New York State Newborn Screening Panel
and Krabbe Disease:
A Systematic Program Evaluation

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Abstract

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The purpose of this study was to conduct a formal program evaluation of the New York State newborn screening for Krabbe disease (KD), a rare neurological disease with variable onset of symptoms to assess 1) the perceptions of stakeholders 2) KD test characteristics, and 3) actual program costs. Using the CDC Framework for Program Evaluation in Public Health, integration of qualitative and quantitative techniques was used to provide a comprehensive evaluation. Stakeholder input was elicited using semi-structured interviews of medical professionals and parents and content analysis of the interview transcripts identified five themes: *Legislative/Political, Unintended Consequences, Knowledge and Science, Communication, and Moral Issues*. Finally, cost and charge data were used to calculate the cost of the KD screening program from the perspective of the State. Triangulation of the results provided the conclusions for practice and policy recommendations. Using the data from the State annual reports of 9 positive KD screening results, sensitivity was calculated at 100%, specificity was 99%, positive predictive value was 5%, negative predictive value was 100% and prevalence was 1/100,000 births. However, the State reports did not include the 19 infants with low enzyme activity and mutations that could develop into later onset forms of KD. When these 19 infants were included, sensitivity, specificity, and negative predictive value remained unchanged; however, positive predictive value rose to 15%, and prevalence increased to 3/100,000 births. The total annual cost of the program from the perspective

of the State was calculated at \$750,652. For parents, the cost calculated from initial newborn screen to neurodiagnostic testing was \$2669/family.

Since 2006, there have been more than 1,000,000 infants screened for KD in New York State. While the screening has identified four infants with the early infantile form of the disease, there have been 24 others identified with low enzyme activity and mutations that may cause later onset forms of the disease, which are poorly understood. This unexpected finding suggests that newborns may be diagnosed with a disease that may not present symptomatically until adulthood. Unfortunately, the current confirmatory enzyme test and neurodiagnostic tests cannot predict onset of disease or severity of symptoms. In addition, the only available treatment, a cord blood transplant, is irreversible, has a high risk of morbidity and mortality, and long term outcomes have not been studied. While the cost of the program from the perspective of the state is not excessive, cost-effectiveness studies are needed to determine the cost of KD screening from the societal perspective, and should include treatment and follow up costs.

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Chapter I: Introduction

Background

Newborn screening programs were first mandated nationally in the 1960's to detect conditions that can be life threatening or cause long-term disabilities. The United States (US) has been the global leader in newborn screening, with the first program implemented in Massachusetts in 1965 (Crowe, 2008). Recognized as a valuable public health service, screening is aimed at providing early intervention or treatment to reduce mortality, morbidity, and other associated disabilities.

Each state in the US is granted the responsibility of governing its own newborn screening program. Policy decisions in each state illustrate differences in community values, political and economic environments, and public health technical abilities and resources (AAP Newborn Screening Task Force, 2000). Screening panels have expanded as technological advances facilitate screening for more diseases. Since 1965, the number of conditions included has increased from one to as many as 57, with considerable variability existing from state to state (National newborn screening and genetics resources center [NNSGRC], 2010). New York expanded its newborn screening program in 2003 to include more than 40 diseases, compared to other states that included as few as eight. In August 2006, New York became the first and only state to include Krabbe disease (KD) in its screening program.

Krabbe disease is a type of leukodystrophy, a progressive neurological disease caused by demyelination of the white matter and peripheral nerves. It is a rare disease, with the incidence estimated at 1 in every 100,000 births (Wenger, Suzuki, Suzuki, & Suzuki,

2001). The disease is detected by measuring the level of the enzyme galactocerebrocidase (GALC) in the blood. Until recently, the more common, infantile onset form of KD was always fatal by 2 years of age. However, there has been some success reported in halting the disease process using umbilical cord blood transplantation (UUCBT) prior to appearance of symptoms (Escobar et al., 2005). Although this treatment option for KD has 10 years of follow-up data regarding physiologic outcomes, quality of life and specific disease morbidity have not been studied.

In 1968, Wilson and Junger developed an initial set of principles for population screening panels including guidance for inclusion of new diseases (Wilson & Junger, 1968). These principles, which are discussed in Chapter 2, have been used by some state legislatures as decision criteria when changing existing panels. However, as patient disease advocacy groups and private industry have gained increasing influence, legislators have other issues to consider. For example, as private laboratories develop and patent tests for rare diseases, adding testing for these diseases to screening panels could be profitable. This has resulted in lobbying by private laboratories, as well as direct marketing to parents (Berg & Fryer-Edwards, 2008). As pharmaceutical companies seek to develop new treatments or modify existing treatments for rare diseases, the pressure to identify new patients at the earliest age may compel their support for addition of testing for these diseases to newborn screening panels. Pressure may also be exerted by the public to employ screening even for conditions that do not have effective or necessary intervention and may otherwise violate the principles of population screening (AAP Newborn Screening Task Force, 2000). This public pressure has occasionally taken

precedence over the established criteria and expert recommendations, further contributing to differences between state panels.

Expansion of screening panels has been an area of concern to health care providers, legislators, and parents for a number of reasons, including: disparities between state programs, cost of testing, ability to pay for treatment of diseases that are diagnosed, and anxiety due to false positive test results. Since no federal entity has the authority to mandate what states will screen for (Green, et al, 2007), the inclusion criteria for the addition of new disorders remain guidelines, and thus, each state's policy decisions remain variable, thus resulting in discrepancies in testing across the US.

Determination of financing of newborn screening programs is also an individual state decision. Varying amounts of federal funding, generally in the form of Title V block grants, are used to augment legislative appropriations and fees. Only Kansas, New York, District of Columbia, and Pennsylvania provide newborn screening at no cost to the infant's family (NNSGRC, 2010). All other states collect fees as the primary source of funding (Johnson, Lloyd-Puryear, Mann, Raskin-Ramos, & Bradford, 2006), ranging in cost from \$15 in Florida to \$139 in Alabama. As genetic science advances and testing becomes possible for more conditions, policy-makers will need objective cost and outcome data to assist in decisions requiring allocation of limited resources.

Statement of the Problem

Since state legislatures have no federal mandate to follow guidelines and public as well as industry pressure can exert undue influence on policy-makers' decisions, a need exists for objective, scientific evidence to help evaluate disorders being considered for

inclusion in screening panels. Illinois, Missouri, and New Mexico have passed legislation to add KD testing to their existing newborn screening panels citing New York State's decision as precedent for their decision (DeLuka & Woolverton, 2008). However, inclusion of KD to New York State's newborn screening panel has not undergone systematic evaluation using objective criteria.

A comprehensive review is needed to provide objective information to stakeholders in New York as well as other states for rational decision-making. In this review, data from the perceptions of stakeholders (including both medical personnel and parents of those infants with positive KD screens) as well as systematic cost analysis would provide important information to decision-makers faced with allocation of scarce resources.

Purpose and Specific Aims

The purpose of this study is to conduct a formal program evaluation of newborn screening for KD in New York State.

The specific aims of this study are to assess:

Aim One

Stakeholder perceptions of the Krabbe Disease screening program in New York State.

Aim Two

The Krabbe disease test characteristics with the most recent data available.

Aim Three

The actual costs of the Krabbe disease screening program.

Significance

Newborn screening is a part of the preventative health system established in all states and territories of the United States. The system involves several components: screening, short-term follow-up, diagnosis, treatment/management, and evaluation. Each of these components has an underlying requirement for education and requires sufficient funding. The effectiveness of any screening program lies in the smooth integration of all components and careful attention to the ongoing evaluation of the screening program, including decisions made to add new tests. Decisions made by each state reflect differences in community values, state political and economic environments, and in public health technical capabilities (AAP Newborn Screening Task Force, 2000). Grosse and colleagues (2005) recommended that any policy decision regarding newborn screening, including assessment of benefits, interventions, risks and costs require evidence-based reviews to be available to the policy makers. Further, it is essential that the actual evaluative process be free from conflict of interest (Grosse, Boyle, Kenneson, Khoury, & Wilfond, 2005).

In August of 2006, New York State was the first state to implement testing for KD. To date, this public health decision has not been formally evaluated. Published information regarding the cost of adding Krabbe disease to the newborn screening panel, from addition of the test to the panel to neurodiagnostic evaluation of those newborns with confirmed low enzyme activity is lacking. The proposed research will provide objective information for public health decision makers considering inclusion of KD in

their newborn screening panel.

Chapter II: Review of the Literature

To provide the background for the development of the Krabbe disease (KD) screening program, the history of population screening, and the development of newborn screening were examined. A variety of evaluation frameworks and cost analysis strategies were examined to determine the method and framework for this study. In this chapter, the following topics are described in detail: population and newborn screening programs, KD, addition of KD to the New York state panel, methods for program evaluation, and cost analysis.

History of Population and Newborn Screening Programs

Research in Norway by Asbjørn Følling in the 1930s indicated that some mentally retarded individuals had very high levels of phenylpyruvic acid in their urine, called phenylketonuria (PKU) (Crowe, 2008). This acid was found only in people who lacked the enzyme to break down phenylalanine, an essential amino acid. High levels of phenylalanine in the body are toxic to the developing brain and cause mental retardation. By limiting the intake of phenylalanine in the siblings of these retarded individuals, Følling was able to demonstrate that the siblings had better health outcomes. Limiting phenylalanine was a concern, since restricting any essential amino acid may impair linear growth and can also cause mental retardation (2008). Therefore, a test that could accurately measure the amount of phenylalanine in the blood was needed. A call went out to scientists to develop a reliable test that could detect high serum levels before toxic buildup occurred. A reliable test would enable physicians to monitor the levels of

phenylalanine and prevent any gross amino acid deficiencies.

It wasn't until the early 1960s that Dr. Robert Guthrie developed a simple test that could detect high levels of phenylalanine using blood collected on filter paper (Guthrie & Susi, 1963). Although the test was not specific and had many false positive results, it was easy to administer and provided information to guide medical practice.

With a link between PKU and mental retardation clearly demonstrated, testing of all newborn infants was proposed to every state in the US. Massachusetts developed the first voluntary newborn screening program in 1962 to test newborn infants for PKU (AAP Newborn Screening Task Force, 2000). This program demonstrated that mass genetic screening was feasible, and other states slowly developed screening programs of their own.

The adoption of the PKU screening by states was bolstered by the federal government sponsored public awareness campaign of the test. Additionally, a federal commission was developed to specifically explore causes of mental retardation (Lesser, 1985). The President's Panel on Mental Retardation was instrumental in providing sufficient information to support passage of Public Law 88-164, which provided funding to academic research centers (AAP Newborn Screening Task Force, 2000) to support scientific research in the study of rare diseases. This funding allowed scientists to develop other tests to add to existing newborn screening programs.

In 1965, New York State followed Massachusetts and enacted Public Health Law 2500a (New York State Newborn Screening Implementation Task Force, 2003), mandating PKU testing of all newborns. By 1973, 43 states had passed similar legislation

mandating the screening of newborns for inborn errors of metabolism, such as PKU, with state health departments having the role of implementing this legislation.

By the 1980's, new techniques such as gas chromatography, enzymatic assays, and radioenzymatic assays had been developed and enabled detection of more inborn errors of metabolism. However, these new tests required plasma or urine instead of blood spots on a Guthrie card and were generally performed only on infants suspected of having an inborn error of metabolism. These methods were time-consuming, expensive, and required that technicians have highly specialized training for proper laboratory analysis of results (Chace, Kalas, & Naylor, 2003) and many states lacked sufficient resources to add these new tests to their screening panels. As a result, states adopted screening differentially, and these differences among programs were first reported by the American Academy of Pediatrics in 1999, raising awareness that variation in screening practices existed (AAP Newborn Screening Task Force, 2000). Today, over 4 million newborns are screened annually in the US for anywhere from 29 to 57 disorders depending on the state of birth (NNSGRC, 2010). This variation is controversial and experts and the public voiced outrage, arguing that a child could live or die depending upon the state in which he was born (Goldberg, 2000).

Newborn screening today.

In the 1990s, researchers at Duke University in North Carolina refined the use of the tandem mass spectrometer (Banta-Wright & Steiner, 2004). The development of mass spectrometry enabled dried blood spots collected in the nursery to be tested in an automated fashion for over 90 disorders (Chace et al., 2003). However, only 71 of these

disorders were determined to be clinically significant. Due to the increased detection of inborn errors of metabolism, many more disorders were being detected in the newborn than had ever been diagnosed clinically (Wilcken, 2008).

Of the disorders detected by mass spectrometry, half require a differential diagnosis, that is, one abnormal analyte can signify the presence of up to three disorders and further testing is needed to obtain a specific diagnosis. Furthermore, treating physicians began to recognize that many metabolic disorders had a spectrum of presentation, from no symptoms at all to classic presentation of severe illness. Without the ability to predict whether a disorder would become symptomatic, specialists were obligated to treat all infants as if they had disease, creating anxiety and hardship for many families (Waisbren et al., 2003).

The concept of infants with a biochemical abnormality on newborn screening and no symptoms of disease has been described by Timmermans and Buchbinder (2010) as “patients-in-waiting.” Follow up of these patients-in-waiting has been cited as “the biggest challenge in newborn screening” (James & Levy, 2006, p. 253).

As a result, today, a comprehensive newborn screening program includes the following: 1) screening of the newborn, 2) follow-up for referral of newborns that test positive for one or more diseases, 3) diagnosis or exclusion of a disease, 4) treatment and management of those with a confirmed diagnosis, and 5) program evaluation and quality assurance (Pass, 2000). Although the screening test alone appears simple, education and training is required for personnel at each point so a program may run efficiently, effectively, and be comprehensive. For example, multiple quality assurance issues must

be considered when developing a newborn screening program, as each step of a program is dependent upon internal standards, skilled preparation of samples, and interpretation of results.

Recognized as a valuable public health service, screening newborns is aimed at secondary prevention, providing early intervention or treatment to reduce mortality, morbidity, and other associated disabilities. With increasing ability to test for more disorders, it is important for decision-makers to have a set of guidelines available to assist in determining those tests that merit inclusion on a newborn screening panel.

Guideline development for newborn screening programs.

As population screening programs grew, national and international agencies began discussing the moral implications of these programs. Concerns were mainly regarding population screening in newborns for adult chronic conditions that had no effective treatment, such as Huntington's disease. To address these concerns, various groups have developed principles to guide population screening (American College of Medical Genetics Task Force, 2006; Committee for the Study of Inborn Errors of Metabolism, 1975; National Institutes of Health, 1997; Therrell et al., 1992; Wilson & Junger, 1968). These guidelines are presented using a format similar to the National Guideline Clearinghouse comparison schema in Table 1, and described in more detail below.

Table 1: Comparison of Guidelines Developed for Population Screening Programs

Guideline Title Date of Release Developer	Methodology: Collection and Selection of Evidence	Methodology: Analysis and Formulation of Recommendations	Recommendations
<i>Principles and Practice of Screening for Disease</i> (1968) World Health Organization (WHO) (Wilson & Junger)	Literature Review	Expert opinion of the authors using the Conference on Chronic Illness guidelines (1951) 1. Validity 2. Reliability 3. Yield 4. Cost 5. Acceptance 6. Follow up services	<ol style="list-style-type: none"> 1. The condition sought should be an important health problem 2. There should be an accepted treatment for patients with recognized disease. 3. Facilities for diagnosis and treatment should be available. 4. There should be a recognizable latent or early symptomatic phase. 5. There should be a suitable test or examination. 6. The test should be acceptable to the population. 7. The natural history of the condition, including development from latent to declared disease, should be adequately understood. 8. There should be an agreed upon policy on whom to treat as patients.
<i>Genetic Screening Programs, Principles and Research</i> (1975) Committee for the Study of Inborn Errors of Metabolism of the	Surveys regarding PKU screening, questionnaires on attitudes of physicians toward genetic screening, review of laws pertaining to screening	Task force meetings, workshops and presentations from 1972-1975 Analysis of quantitative data collected from surveys and questionnaires	<ol style="list-style-type: none"> 1. Genetic screening should have evidence of public benefit & acceptance, including medical practitioner acceptance. 2. Feasibility of test has been investigated – with benefits outweighing cost, in all aspects associated with NBS programs. 3. Pilot studies of new tests have shown the above. 4. Means exist to evaluate effectiveness and success of each step.

Guideline Title Date of Release Developer	Methodology: Collection and Selection of Evidence	Methodology: Analysis and Formulation of Recommendations	Recommendations
National Academy of Sciences (NAS)			<ol style="list-style-type: none"> 5. NBS must be part of an agency representing the public and health professions. 6. Public representation must be part of policy decisions. 7. Aims of genetic screening programs must be clearly formulated and publically available 8. Genetic screening programs should not be made mandatory without significant oversight by a Federal Committee for the purpose of evaluating new tests.
<i>Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing</i> (1997) National Institutes of Health (NIH)	Task Force review of briefing materials, presentations, laws and regulations pertaining to genetic testing, and literature	Task force meetings from 1995-1997 Voting and non-voting government agency liaisons reviewed briefings and attended meetings and representations until consensus reached on the final report and recommendations.	<p>Focused on review of genetic testing and ensuring development of safe and effective tests.</p> <ol style="list-style-type: none"> 1. Strongly advocated informed consent for ALL genetic testing. 2. Newborn screening tests must have safe and effective interventions for treatment of disorder screened for. 3. Testing children for adult-onset diseases should not be undertaken unless there is direct medical benefit to treating before adulthood. 4. All genetic testing should be confidential and results must not lead to discrimination by any third party. 5. Consumers should be involved in policy decisions. 6. Providers must be knowledgeable about the disorders being tested.

Guideline Title Date of Release Developer	Methodology: Collection and Selection of Evidence	Methodology: Analysis and Formulation of Recommendations	Recommendations
<i>US Newborn Screening System Guidelines II: Follow-up of Children, Diagnosis, Management, and Evaluation Statement of the Council of Regional Networks for Genetic Services (1999)</i> <i>Council of Regional Networks for Genetic Services (CORN)</i>	Literature Review	Authors reviewed all current guidelines and literature pertaining to NBS systems results management Used the five parts of a Newborn Screening System to establish guidelines for each condition and overall system: 1. Screening 2. Follow-up 3. Diagnosis 4. Management 5. Evaluation	Focused on guidelines for effective NBS programs – anticipating the expansion of NBS to include presymptomatic screening. Evaluation of the overall NBS system: 1. Incidence of each disorder. 2. Effectiveness & speed of identifying affected infants & entering them in comprehensive care. 3. Quality of screening & diagnostic tests. 4. Monitoring and outcome assessment. 5. Costs for operating entire system. 6. Costs of each component.
<i>Newborn Screening: Toward a Uniform Screening Panel and System (2006)</i> <i>American College of Medical Genetics (ACMG)</i>	Tier 1: Development of a data collection instrument Tier 2: Evidence base for conditions established and decision-making algorithm for reassessment was developed	Convened the Newborn Screening Expert Group of participants with expertise in areas of: subspecialist and primary care medicine, health policy, law, ethics, public health and consumers Survey results for each condition scored, then entered into the decision-making algorithm	Defined 29 core conditions and 25 secondary conditions to include on NBS panels 1. Mandate screening for all core panel conditions defined in the report. 2. Mandate reporting of all secondary conditions and abnormal results of significance (i.e. carrier status). 3. Maximize the use of multiplex technologies; and 4. Consider that the range of benefits realized by NBS includes treatments that go beyond an infant's mortality and morbidity.

The first set of guidelines, written by Wilson and Junger, (1968) was relevant to newborn screening programs because they addressed the moral focus of the interests of the child, from the perspective of medical need and benefits to the newborn. These principles provided an underlying framework for the difficult task of adding new tests to screening panels as technology grew. These 1968 guidelines were seminal and cited in those that followed (Wilson & Junger, 1968).

In 1975, the Committee for the Study of Inborn Errors of Metabolism of the National Academy of Sciences published a set of recommendations for genetic screening programs that suggested formation of a federal agency to provide oversight of genetic testing. This committee would have public representation and would review the feasibility, validity and use of new tests. The committee asserted that genetic screening tests should not be adopted without medical acceptance of new tests (Committee for the Study of Inborn Errors of Metabolism, 1975).

In 1985, the Council of Regional Networks for Genetic Services was created to provide a forum for discussion among groups concerned with the public health aspects of newborn screening (Therrell et al., 1992). The council included representatives of state laboratories and administrators from each geographic region of the US. The council published guidelines in 1990 to specifically address newborn screening programs. The recommendations for adding or deleting tests from screening programs were that the process should be logical and systematic, and decisions should consider population demographics, methodology of testing, outcome of testing, and economics. Further, the recommendation was to include screening for only those disorders with effective and

accessible intervention. Scarce funding resources were addressed in these guidelines, suggesting that a uniform method of determining program costs should be developed nationally.

The Task Force on Genetic Testing, funded by the National Institutes of Health, was created in 1995. This group published their report of suggested guidelines in 1997 (National Institutes of Health, 1997). These guidelines for genetic testing were an attempt to address advancing technology by providing characteristics of tests identifying areas requiring stringent scrutiny by scientists, health care providers, and policy-makers. Although the task force encouraged development of tests for rare diseases, they advised caution regarding tests for conditions with no safe and effective clinical interventions. The committee placed emphasis on the importance of full informed consent for genetic testing, provided by the person administering the test. The task force also acknowledged the broadening scope of those who could be affected by genetic testing, from the asymptomatic infant, who could develop disease as an adult, to extended family members, to the ethnic group of the infant. The recommendation was to increase training and education of those providing genetic testing. This task force specifically recommended a formal charter for the Secretary's Advisory Committee on Heritable Diseases of Newborns and Children to review the development and make recommendations for new screening tests for population screening programs.

In 2000, based on the recommendations from the Task Force on Genetic Testing, the Maternal and Child Health Bureau Division of the Department of Health Resources and Services Administration (HRSA) commissioned the American College of Medical

Genetics (ACMG) to create a task force. This task force was asked to conduct a complete analysis of the scientific literature on the effectiveness of newborn screening, gather expert opinion to delineate the best evidence for screening specified conditions, and to develop recommendations focused on newborn screening, including the development of a uniform condition panel (ACMG Task Force, 2006). A survey was developed with scoring criteria in an attempt to create a ranking system for 84 disorders that were either currently in state newborn screening panels, or being considered for addition to existing panels. The survey included 3 categories for each disorder: 1) clinical characteristics of the disorder; 2) analytical characteristics of the screening test; and 3) diagnosis, management and treatment of the disorder, which included both acute exacerbations and chronic care phases. Nineteen criteria for scoring were included within the 3 categories. This scoring system was developed to recognize the strengths and limitations of each condition and summarized them in a ranking system for a total of 2100 possible points. This way, a condition could have a low score in one category, but high in another category. However, this scoring system has been criticized as not conforming to contemporary evidence-based process, as well lacking transparency (Moyer, Calonge Teutsch, & Botkin, 2008). After a pilot study, the survey was distributed to newborn screening experts and advocates for their opinions. After analysis of the 300 responses, the disorders were divided into three groups: High scoring (1200-2100), Intermediate scoring (1000-1199) and low scoring (<1000). Conditions scoring below 1000 were not considered appropriate for screening, the conditions with scores >1200 were considered appropriate for inclusion in newborn screening panels, and the intermediate scoring

conditions were considered as secondary targets (ACMG Task Force, 2006). This resulted in a core panel of 29 disorders, with an additional 25 secondary target disorders that could be detected by differential diagnosis from the 29 core disorders. The American Medical Association published a report criticizing the survey criteria, the methodology of survey distribution used by the ACMG, and the lack of cost-effectiveness data to support the recommendations made by the group (American Medical Association, 2006). Another report published by the Hastings Center on behalf of the United States Preventive Service Task Force criticized the ACMG survey for not conforming to an evidence-based process, questioning the methodology used for evaluation of the conditions on the panel, and lack of consideration to the harms that a false positive screening result could cause when identifying infants who screen positive but have no symptoms of disease (Moyer, Colange, Teutsch, & Botkin, 2008).

The ACMG survey criteria further broadened the rationale for newborn screening. Previous guidelines focused on testing for disorders to prevent death and disability in an affected child. The ACMG criteria defined benefits for the affected child to include burden of disease and potential for overall improvement with early intervention with or without a requirement for effective treatment (Grosse et al., 2005). Benefits to families were also expanded to include timely knowledge of a disorder to avoid the diagnostic difficulties accompanying many of the metabolic disorders. This benefit was given as much weight in the scoring system as prevention of mortality (Grosse et al., 2005).

Despite differing opinions and criticism of the ACMG report, there was nearly universal acknowledgement by professional organizations, parent advocacy groups,

experts in the field, and public policy decision makers (American Medical Association, 2006) that standardized newborn screening criteria was needed. The ACMG uniform screening panel was adopted by the Secretary's Advisory Committee on Heritable Diseases in Newborns and Children (Secretary's advisory committee on heritable disorders in newborns and children, 2009). This committee was chartered to evaluate new disorders nominated for addition to the uniform panel, perform an extensive evidence review, and to send recommendations to the Secretary of Health and Human Services (Green, et al., 2007).

Reports submitted by this committee have provided evidence to Congress that facilitated passage of the Newborn Screening Saves Lives Act into Public Law 110-204 in May 2008. The Newborn Screening Saves Lives Act was passed authorizing \$45 million each year in funding for education and outreach on newborn screening, to assist states in providing coordinated follow-up care after screening, and grant funds for purchasing necessary equipment to expand screening capabilities (Dodd, 2008). However, for fiscal years 2009 and 2010, this law received appropriation of just \$10 million per year in the Federal budget (Williams, 2009). While authorizing funding, no punitive language was included for states opting to test for more or less than the suggested 29 core disorders; thus, this law remains a guideline.

The ACMG guidelines (2006) added the criterion of economic evaluation when considering addition of a new test to a newborn screening panel. Despite the publication of many economic analyses of newborn screening programs, evidence of benefit has been debated. Grosse (2005) asserts that while newborn screening programs have certainly

been accepted as cost-effective; the expansion of existing screening panels may not be cost saving. Economic studies seldom fully address the issues of costs and consequences and the influence they may have on expansion of newborn screening panels (Grosse et al., 2005). The standard economic analyses also include decision parameters that fall short of consideration of all costs included in the incorporation of a new test into a screening panel (Hubbard, 2007). In this dissertation, efforts will be made to include the direct costs and consequences of KD screening from the perspective of the State.

Overview of Krabbe Disease

Krabbe disease (KD), also known as globoid-cell leukodystrophy, is an autosomal recessive disorder due to the deficiency of a lysosomal enzyme galactocerebrocidase (GALC), which results in failure of the myelination process of the central and peripheral nervous system. Incidence of KD has been estimated at 1 in 100,000 births in the US. First described in 1916 by Dr. Knud Krabbe (Krabbe, 1916), the classic disease (infantile form) causes rapid, progressive neurologic deterioration and death. Children who inherit the infantile form of the disease develop symptoms before 6 months of age. Symptoms include irritability, dysphagia, progressive spasticity, mental deterioration, blindness, deafness, and seizures. Children affected with infantile KD generally die before 2 years of age (Wenger et al., 2001).

Two other forms of KD are known to exist, late infantile onset, which presents with symptoms after six months of age, and juvenile/adult onset, with symptoms appearing from four years of age to adulthood. All patients with KD have GALC activity less than 0.15 nmol/hr/mg protein, white matter changes in the brain on magnetic

resonance imaging (MRI), weakness, loss of motor skills, and may present with sudden onset of vision loss, and burning paresthesias of the extremities (Suzuki, 2003). However, the late infantile and juvenile/adult onset forms are highly variable in both disease symptom presentation and severity. This creates a diagnostic problem for the clinician, as the symptoms of KD also present in other neurologic conditions, like multiple sclerosis, other leukodystrophies and some ataxias (Arenson & Heydemann, 2005; Morse & Rosman, 2006; Srinivasan, Coleman, & Kornberg, 2008) . Thus, the possibility of KD is likely to be dismissed in favor of the more common diagnosis.

Management and treatment of Krabbe disease.

In the past, once KD was diagnosed, the only available option was symptom management until death occurred around two years of age. Experimental allogenic bone marrow transplantation had been published as treatment in case reports, but with little success in alleviation of symptoms (Krivit, Shapiro, & Peters, 1998). This treatment required an appropriately matched donor, which was often unavailable. Also, bone marrow transplant requires radiation to ablate the immune system, not an option for infants less than one year of age, since this could cause severe damage to a newborn's brain.

In 2000 the National Heart, Lung and Blood Institute of the National Institutes of Health sponsored a multi-center study to investigate the safety and feasibility of using partially matched, banked, unrelated donor umbilical cord blood stem cells for transplantation (UCBT) in children and adults with lysosomal storage diseases (Martin et al., 2006). One of these centers, Duke University, conducted a matched cohort control

study to evaluate UCBT for KD (Escolar et al., 2005). Twenty-five infants with infantile KD (11 asymptomatic newborns and 14 symptomatic infants) received UCBT after myeloablative chemotherapy instead of radiotherapy for ablation. The control group was a historical cohort of untreated patients obtained from a disease registry (n=190). The asymptomatic infants were siblings of children who had died from or had been diagnosed with KD. Endpoint measurements chosen were survival, donor-cell engraftment, and normal GALC levels. In the untreated historical cohort, all infants died by age 96 months. Over a 3-year average follow up period, all the asymptomatic children met every endpoint. Among the symptomatic recipients, 43% survived (6 out of 14) and of those who survived, 100 % had successful donor-cell engraftment. The infants in the asymptomatic group demonstrated improved neurologic and neurodevelopmental outcomes compared to the symptomatic group.

Although the study results were favorable to those who received a transplant prior to onset of symptoms, ongoing issues requiring medical attention remained. Eleven of the 25 children transplanted developed graft versus host disease, all of the children developed some degree of gross motor deficit, and all the children were below the fifth percentile in height and weight despite adequate nutrition (Escolar et al., 2005).

While some benefits of early treatment have been documented, the data and treatment options are not clear-cut. Other than mentioning the number of children who developed graft versus host disease, the degree to which the transplant affects the infant and family has not been discussed. While gross motor development is mentioned as a concern, the ongoing progression of KD has not been fully explored, nor is the severe

growth retardation of all children receiving UCBT. Escolar, et al. (2009), reports that all the infants treated in the original UCBT treatment study develop some degree of motor function, ranging from mild to severe, but asserts their cognitive function is preserved. Additionally, controversy exists among the authors of the study done at Duke regarding the developmental components of the study. One author suggests the portrayal of developmental progress of the asymptomatic group is somewhat slanted, that these children appear obviously abnormal, and that cognitive delays will become more evident as these children entered school (Friedman, 2008).

Duffner, et al (2009) published a summary of long-term outcomes of the children from the Duke study who were transplanted presymptomatically. The summary findings included the following: 1) the transplant procedure carries a 15 % mortality rate; 2) all the children slowly develop progressive neurologic deterioration over time, ranging from developmental delay, increasing spasticity, loss of motor milestones and language deficits; and 3) all had height and weight below the third percentile for sex and age (Duffner, Caviness et al., 2009). These issues point toward the lack of knowledge surrounding the natural course of the disease despite available treatment.

Quality of life and cost have not been studied regarding the treatment and sequelae of treated KD. There is little information known about the late onset forms of the disease, or the outcomes of very low enzyme activity, which is currently being diagnosed because of newborn screening in New York State. The natural course of the later onset forms of KD is relatively unknown, and currently, the evidence regarding successful treatment for this type of KD is mixed. Policy decision makers and parents are

presented with information that is not comprehensive; therefore, more data are needed to better inform decision makers.

Testing for Krabbe disease.

Individuals with all forms of KD will have low GALC enzyme activity level (< 0.15 nmol/h/mg protein) in leukocytes isolated from whole blood (Galvin-Parton, 2003). While the biochemical diagnosis of this disease is not difficult, due to the low incidence of the disease, as well as the belief among many clinicians that KD only presents in the severe infantile onset form, few clinicians consider this testing when neurological symptoms are present. Furthermore, symptoms of KD are similar to many more common neurologic disorders; thus, other diseases are often ruled out before specific testing is ever considered. Measuring GALC enzyme activity provides only part of the diagnosis. To better predict the type of KD, an analysis of the genetic sequence should also be performed.

The deoxyribonucleic acid (DNA) sequence for GALC was mapped in 1993 and is located on gene 14q31 (United States National Library of Medicine & National Institutes of Health, 2009). Currently, over 60 mutations are recognized to cause some decrease in activity, and the most common mutation causing infantile onset KD is a homozygous 30kb deletion (Suzuki, 2003). Large deletions of the GALC gene are known to cause disease, but it remains unclear which combinations of mutations cause later onset disease. Unfortunately, the genotype is not indicative of disease severity, since family members having the same mutations may present phenotypically with very different symptoms and severity (Wenger, Rafi, Luzi, Datto, & Costantino-Ceccarini,

2000).

In 2004, Li and colleagues presented the results of their multiplex screening model for five lysosomal storage diseases, including KD, using dried blood spots from newborn screening cards (Li, Brockmann, Turecek, Scott, & Gelb, 2004). By rehydrating the dried blood spot with a buffer solution containing substrates of the enzymes of interest, multiplex testing with tandem mass spectrometry was then possible.

Testing for the GALC enzyme testing was 100% sensitive using this method (Li et al., 2004). However, problems arose with the specificity of the testing, such as overlap between the lysosomal storage conditions, which then required further enzymatic testing to confirm a diagnosis. In practice, this further testing translates into increased technician time, and therefore, increased test cost. Problems were also reported with blood samples stored at temperature extremes resulting in false positive results, requiring increased time for personnel notifying parents of newborns, as well as increased confirmatory testing costs (Li et al., 2004). Another quality concern was that the research had been conducted using a relatively small number of samples. In this study, only 31 dried blood spot samples were processed manually over a period of days. There had been a concern that the much higher number of samples being processed in a newborn screening program could interfere with the accuracy of the test results (Li et al., 2004).

New York State's Wadsworth Laboratory processes approximately 500 dried blood spots daily, using an automated process. The technique described by Li et al. (2004) was not feasible to accommodate the volume of blood spots processed in New York State. A team at Wadsworth laboratory attempted to modify Li's technique, to only

test for KD, and to increase throughput (Orsini et al., 2009). This modified technique was validated in a one-year pilot study conducted using 139,000 randomly collected, de-identified newborn dried blood spot punches and dried blood spots of persons with KD as positive controls. The method provided 100 % detection of all positive controls, as well as detection of one anonymous infant who was later diagnosed with KD. Based on these data, the cut-off value for a positive KD screen was also determined.

Addition of Krabbe disease testing to the New York State panel.

The impetus for inclusion of this test in the New York screening panel came from the KD advocacy group, Hunter's Hope (www.huntershope.org). The spokesperson of this group was Jim Kelley, a former Buffalo Bills quarterback, whose son Hunter died of KD (Editors - Genomics & Genetics Weekly, 2004). The argument for adding KD to the New York State newborn screening panel was as follows: the results of the Duke study suggested favorable outcomes in presymptomatic infants treated with cord blood transplant, and a screening test was available that used the dried blood spots collected in the newborn nursery. Infants with KD could now be identified presymptomatically, so treatment could be pursued in a timely manner. Without screening, KD diagnosis was unlikely to occur until after symptoms had appeared.

In January of 2005, Governor Pataki announced the decision to include KD screening to the New York newborn screening panel (Pataki, 2005). Prior to this decision, a scientific task force had been convened to review the evidence from the then unpublished Duke treatment study, the results of pilot testing in New York using the methodology proposed for screening the newborn blood spots, and the overall utility of

inclusion of the KD on the panel. The task force was comprised of metabolic specialists, genetic specialists, neurologists, and pediatricians, all from New York State, who unanimously recommended against inclusion of the test on the panel (Pacenza, 2006). Despite the task force recommendation and prior to any published evidence regarding treatment, on January 18, 2006, section 69-1.2 of NYCRR 10 of Public Health Law §2500-a, was amended by emergency rule. The finding of necessity provided in the Emergency Rule legislation to add Krabbe disease to the newborn screening panel was, “Preservation of public health,” (Expansion of the New York State newborn screening panel, 2006. p.6). Under the heading of *Alternative Approaches* on page 9 of the New York State Register, February 8, 2006, it is stated:

Potential delays in detection of Krabbe disease until onset of clinical symptoms would result in increased infant morbidity and mortality, and are therefore unacceptable. Given the strong indication that treatment is available to ameliorate adverse clinical outcomes in affected infants, the Department has determined that there are no alternatives to requiring newborn screening for this condition. (p. 9)

It remains unclear whether the decision to include KD to the New York screening panel meets the goal of preventing irreversible neurological damage or developmental delay as stated by the New York State Newborn Screening Task Force (2003).

Nonetheless, inclusion of the test by New York State has been cited as evidence to support its inclusion on other state newborn screening panels. To date, Illinois, Missouri, and New Mexico have added KD screening to their newborn screening panels, based in part on the success of the New York State program (Pressey, 2010; *Newborn screenings*

set to be expanded, 2009; Associated Press, 2010).

Recently, after review of existing evidence, three years after New York added KD to the newborn screening panel, the Secretary's Advisory Committee for Heritable Disorders of Newborns and Children recommended not adding KD to the core panel of newborn screening tests (Howell, 2009). The rationale provided for this conclusion was insufficient evidence in several areas: the impact of a positive screen on families, diagnostic difficulty in identifying affected infants, and issues regarding treatment outcomes (Kemper et al., 2010). A systematic program evaluation is the first step to provide information needed to better inform decision-makers both in New York as well as other states and countries.

Overview of Krabbe disease screening in New York State.

When the New York State Health Department implemented KD screening, it was estimated that 25 newborns would be referred annually for confirmatory testing of the severe infantile onset form of the disease, and 3 would be confirmed with disease (New York State Department of Health, 2003). The later onset forms of the disease, while known, were thought to be so rare that no consideration to their detection was given. In practice, however, more infants have been identified with very low enzyme activity and no symptoms of disease than infants with the early onset form of KD (Duffner, 2010).

Counseling families of these infants may be problematic for the metabolic specialists, as little is known about the onset, natural history, or treatment of later onset forms of KD. Parents of newborns diagnosed with very low enzyme activity may be left with an increased level of anxiety over the future of their child's health, a condition that

may increase use of health care resources even when their child appears completely healthy (Waisbren et al., 2003). These families are left with diagnostic uncertainty and may be unclear about whether or not their child will develop KD or unsure if their child even has a disease (Timmermans & Buchbinder, 2010). Therefore, the criteria of “effective, available treatment, and adequate understanding of the natural history of the condition, including development from latent to declared disease,” set by Wilson and Junger (1968) becomes an area of controversy regarding the inclusion of this disease in newborn screening panels. This dissertation addresses the gaps in the literature by assessing the perceptions of the KD screening program from the perspective of both the parents and medical specialists.

After KD was added to the New York newborn screening panel, a consortium was formed to implement screening and review the progress of the program. The rationale for the formation of the consortium was the different method of confirmatory testing and the irreversible and more dangerous treatment required for KD compared to other inborn errors of metabolism on the panel. The Krabbe Disease Consortium is a multidisciplinary group consisting of neurologists, metabolic specialists, hematologists, nurse practitioners, genetic counselors and laboratory scientists directly involved with newborn screening in New York State. The consortium is funded by the Hunter’s Hope Foundation (Duffner, 2008), the nonprofit arm of the parent advocacy group. The Krabbe Disease Consortium has met every six to eight months since KD screening was legislated to address issues arising from testing (2008). As pediatric nurse practitioner at the Mount Sinai Medical Center specialty care center, all meetings were attended by the investigator (RS).

There have been several changes in the KD program as a result of these meetings, notably the use of a single confirmatory enzyme testing lab, reconsideration of the “low risk to develop disease” category, and minor changes in the follow up protocol (Duffner, 2010). While minutes are taken during these meetings, they have not been reliably distributed (J. Pellegrino, J. Kwon, G. Arnold, personal communication, April 16, 2010)

A clinical protocol was developed by consensus of the consortium to provide ongoing evaluation of children who had confirmed low enzyme activity (Appendix 2). This clinical protocol was developed using expert opinion to provide a more standardized approach for further evaluation and determination of recommendation for transplant. However, the protocol has not been validated, and is not adhered to consistently in the eight specialized care centers, often due to parental refusal of the invasive tests (Duffner, 2010).

A point system based on the results of the activities in the protocol was also established to guide referral for UCBT. The follow up protocol and point system are found in Appendix 2. However, there is disagreement regarding the actual effectiveness of the treatment (Friedman, 2008). Furthermore, UCBT is invasive, irreversible, and the associated mortality rate is high. The long-term effects of UCBT for the early onset form of the disease have not been sufficiently studied, and questions remain about the true effectiveness of the only available treatment.

Detailed description: Krabbe disease screening program and goals.

To provide a detailed description and understand the goals of the KD Screening program in New York State, a content analysis of available documents was conducted.

The documents providing the data for content analysis came from several sources, including: written and electronic publications from Wadsworth Laboratory for the public, health care providers, and other laboratories; New York State Public Health Law §2500-a; minutes from the KD consortium meetings; the emergency rule proceedings published in February 2006; other published descriptions of the New York State KD screening, and testing methods. All documents were entered into the NVIVO 8 ® (QSR International Pty Limited, 2008) software program for data storage and content analysis. What follows is a synthesized description of the New York State KD screening program and programmatic goals.

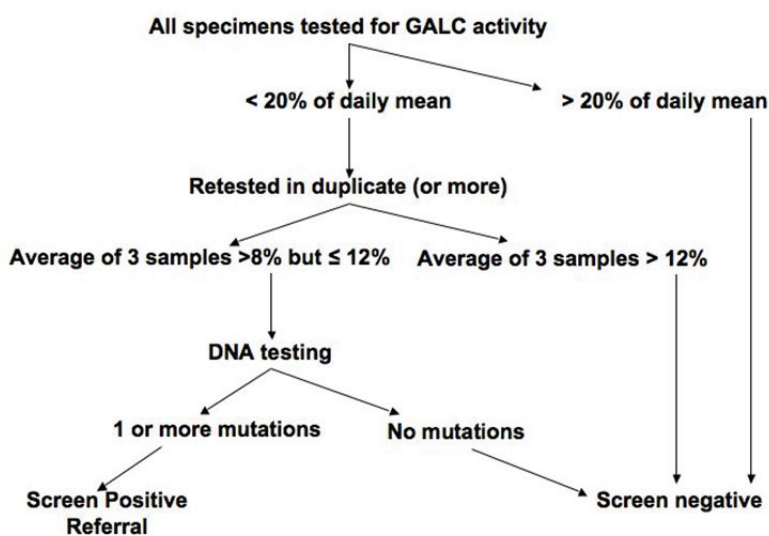
All infants born in New York are screened for 46 disorders 24 hours after birth (New York State Department of Health, 2006b). The aim of this screening according to the State Legislature is to identify New York's youngest citizens with serious, but treatable neonatal conditions and assure timely referral for medical intervention (Expansion of the New York State newborn screening panel, 2006). Screening is mandatory; however, a parent may choose to opt out of screening based on religious objection (Testing for phenylketonuria and other diseases and conditions, 1997). Providers are required to notify parents that the screening is being done and provide education about the screening to the parents. To meet this requirement, a pamphlet is available explaining the screening in English, Spanish, French, Haitian Creole, Chinese, Russian, and Vietnamese (New York State Department of Health, 2006b). Blood is collected via heelstick in the nursery, placed on a Guthrie card, dried, and sent to Wadsworth Laboratory in Albany, NY for processing (New York State Newborn

Screening Implementation Task Force, 2003).

At the Wadsworth Laboratory, the dried blood spot punches are processed using 3 different methods. For KD, tandem mass spectrometry is used to identify the GALC activity (New York State Department of Health, 2003). The value chosen for a positive screen was the average percentage of daily mean activity of GALC over 3-day period. The cutoff point determination for a positive screen for KD was set conservatively to minimize the potential for false negative results. If the GALC activity is $\leq 12\%$, a secondary analysis is performed. This secondary analysis looks for mutations and polymorphisms associated with KD, and was instituted to reduce the number of false positive results (Orsini et al., 2009). The screening algorithm for KD is shown in figure 1 and is discussed below.

Figure 1
Krabbe Disease Screening Algorithm

Krabbe Screening: Cutoffs and Testing Algorithm



Orsini, J. (2010, December). Krabbe Disease Consortium Meeting, New York, NY

When an infant screens positive for KD, either the infant's pediatrician of record or a representative from the metabolic referral center notifies the parents and an appointment is made for confirmatory testing. At the metabolic center, the infant receives a full physical examination, and an explanation of genetic inheritance, mutations, and KD is provided to the family. Five milliliters of blood is collected from the infant and sent for confirmatory enzyme activity at the Lysosomal Diseases Testing Laboratory at Thomas Jefferson University in Philadelphia, PA (New York State Department of Health, 2003). After signing informed consent for genetic testing, blood spots are collected from both parents and the infant and sent to Wadsworth laboratory for deoxyribonucleic acid (DNA) testing of the GALC sequence and to assure correct identity of the infant. Enzyme activity results are available in 3 days and the parents are contacted with the results. DNA results are provided at a later date to the metabolic specialist by Wadsworth laboratory, and parents are informed of their results by the metabolic center.

If the confirmatory enzyme activity is less than 0.3 nmol/mg protein/hour, the infant is admitted to the hospital for a neurology evaluation, lumbar puncture, magnetic resonance imaging (MRI) with sedation, visual evoked potential (VEP), and a nerve conduction velocity test (with F-wave) (Duffner et al., 2009). If the infant's DNA sequence reveals two 30kb deletion mutations, or the enzyme activity is less than 0.15 nmol/hr/mg protein, a consultation with an oncologist for UCBT evaluation is ordered, and human leukocyte antigen (HLA) typing is conducted for the infant and both parents (New York State Department of Health, 2003). At this point, parents are informed about the options available for treatment, and are also given the option of no treatment.

From the perspective of the State, the goal of newborn screening in New York is found on the Wadsworth Laboratory website, as well as in the Guide for Health Professionals (2003). The goal is stated:

The goal of newborn screening is early identification of children at increased risk for selected metabolic or genetic diseases so that medical treatment can be promptly initiated to avert metabolic crises and prevent irreversible neurological and developmental sequelae. (p.1-1)

In the educational pamphlet provided to parents (New York State Department of Health, 2006b), the goal of newborn screening is stated in a slightly different manner. The goal is, “To help ensure that your baby will be as healthy as possible,” and further asserts, “With early diagnosis and medical treatment, serious illness can often be prevented.” (para 1)

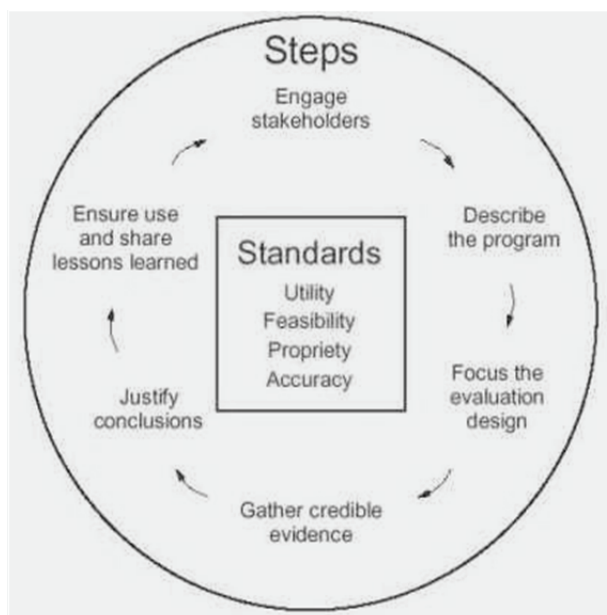
Overview of Program Evaluation

Evaluation is the systematic investigation of a product or activity to determine its merit (quality), worth (cost-effectiveness), and significance (importance). When applied to organized activities intended to promote and protect health, an evaluation usually determines whether specified "outcomes" or health goals were reached and whether or not those results can be attributed to the program (Center for Health Improvement, 2008). Evidence based program analysis is grounded on the availability and accessibility of information and how context affects the evidence used (Dobrow, Goel, & Upshur, 2004). The framework of evaluation should be chosen to best address the intended audience of

results. A number of evaluation frameworks were reviewed to determine relevance for this study (Center for Health Improvement, 2008; Centers for Disease Control and Prevention, 1999; Stufflebeam, 2003).

In 1977, the Centers for Disease Control and Prevention (CDC) convened a working group to develop a framework that could be used to provide a comprehensive and systematic evaluation method for public health programs. In the development of this framework, existing evaluation frameworks were reviewed. The result of this workgroup's efforts was the CDC Framework for Evaluation of Public Health Programs (1999). The framework is depicted graphically in figure 2.

Figure 2: CDC Framework for Program Evaluation in Public Health (Centers for Disease Control and Prevention, 1999)



Standards and steps are defined for those performing a program evaluation,

specifically a public health program, making it ideal for evaluating the addition of KD screening to the New York State newborn screening panel. Standards are placed in the center of the framework graphic to represent their application throughout the entire evaluation. They provide the investigator with guidelines to assure a thorough and balanced evaluation. Standards of program evaluation are used to answer the question, “Will this evaluation be effective?” (Milstein & Wetterhall, 1999). The standard of utility ensures the information collected during the evaluation will be valuable and timely. Feasibility represents the practicality of the evaluation, that it is conducted in a nondisruptive and frugal manner. Propriety standards ensure that the evaluation is conducted in a legal, ethical manner, with regard to the rights of those who participate in the process. Finally, the standard of accuracy promotes the transparency of methods, data collection and reporting of accurate information.

For each of the six steps, suggested activities and evaluation techniques are defined in a systematic, evidence-based fashion. The use of several methodologies is recommended to complete each of the steps, resulting in a thorough, systematic evaluation. Integration of qualitative and quantitative information has been thought to increase the likelihood that evidence will be balanced (Centers for Disease Control and Prevention, 1999).

An important part of this evaluation framework involves engagement of the stakeholders. Stakeholders are chosen to represent the groups recommended by the authors of the CDC Framework (1999). These recommended stakeholder groups are: 1) Those involved in program operations, 2) Those served or affected by the program, and

3) Those in a position to make decisions about the program. The third group of stakeholders generally includes legislators, and may also include stakeholders from the other two groups, if they have input into the decision making process.

As outlined by the framework, a complete program description includes: the need for the program, the context within which the program operates, explanation of program activities, and description of resources. The description provides a synthesis of the main program elements to display how the program is supposed to work and the intentions, focus, or communication trends of any individuals, groups, or institutions involved with the program. The detailed description of the program was conducted as preliminary work in the development of this dissertation and was reviewed earlier in this chapter.

To focus the evaluation design, a thorough description of the methodology and rationale for choosing a particular method must be provided. The choice of methodology and process of data analysis drives the collection of credible evidence. The methods chosen for this dissertation are discussed in Chapter 3.

The ACMG guidelines (2006) added the criterion of economic evaluation when considering addition of a new test to a newborn screening panel. Despite the publication of many economic analyses of newborn screening programs, evidence of benefit has been debated. Grosse (2004) asserts that while newborn screening programs have certainly been accepted as cost-effective; the expansion of existing screening panels may not be cost saving. Economic studies seldom fully address the issues of costs and consequences and the influence they may have on expansion of newborn screening panels (Grosse et al., 2005). The standard economic analyses also include decision parameters that fall

short of consideration of all costs included in the incorporation of a new test into a screening panel (Hubbard, 2006). Cost studies are one way to evaluate the value of adding tests to newborn screening panels. In this dissertation, efforts will be made to include the direct costs and consequences of KD screening from the perspective of the State.

The interpretation of the data must be adequately explained. The results of the analysis are presented in Chapter 4 and then discussed in Chapter 5. The framework recommends that the process should be transparent and lead to conclusions and recommendations that are useful to the stakeholder groups.

The last step of the evaluation is to ensure its use. To accomplish this, conclusions will be made available to stakeholders and to the public by presentation at national meetings and publication of the evaluation in academic journals. The dissemination to date and future plans are discussed in Chapter 5.

The CDC Framework provides the basis for this evaluation of the KD screening program addition to New York State's newborn screening panel. Compared to other evaluation methods, this framework is comprehensive and systematic, as well as focused toward public health programs.

Summary

The addition of screening for KD to the New York State newborn screening panel in 2006 has not been formally evaluated in a systematic way. This is problematic, given that other states have added or are considering addition of this screening test based only on the fact that New York State provides this screening. No published information was

found regarding Krabbe screening effectiveness or the costs involved with the addition of the screening to the established screening panel. No published information exists for decision makers in other states to consider when deciding on utilization of already scarce resource. This research will serve to provide this information.

Chapter III: Design and Methodology

The aims of the study were to assess: 1) stakeholder perceptions of the Krabbe Disease screening program in New York State, 2) the KD test characteristics with the most recent data available, and 3) the actual costs of the KD screening program. The data sources, data collection sites, and methodology for each study aim will be discussed in detail in this chapter. Briefly, a mixed methodology using the qualitative techniques of semi-structured interviewing, constant comparison and thematic content analysis and quantitative techniques of calculating test result characteristics and a simple cost analysis was conducted to provide a rich evaluation of the KD screening program.

Study Design – Guiding Framework

To fully evaluate KD as the most recent addition to the New York State newborn screening program, a formal, systematic program evaluation was performed. The Framework for Program Evaluation in Public Health developed by the CDC (Milstein & Wetterhall, 1999) discussed in Chapter 2, was used to guide the research. The steps and standards are described in figure 3, which has been adapted to reflect their specific application to this study.

Figure 3: *CDC framework steps and standards for effective evaluation*

Steps in Evaluation	
<i>Step 1: Engage stakeholders</i>	<ul style="list-style-type: none"> -Persons involved in the program – Health Care Providers, Program directors -Persons affected by the program – Parents -Program decision-makers– Program directors, Legislators
<i>Step 2: Describe the program</i>	<ul style="list-style-type: none"> -Chapter 2 - Review of the Literature -Chapter 2 - Description of Krabbe Disease Screening and Program Goals
<i>Step 3: Focus the evaluation design</i>	<ul style="list-style-type: none"> -Chapter 3 - Design and Methodology
<i>Step 4: Gather credible evidence</i>	<ul style="list-style-type: none"> -Chapter 3 - Design and Methodology -Chapter 4 - Results
<i>Step 5: Justify conclusions</i>	<ul style="list-style-type: none"> -Chapter 4 - Results -Chapter 5 - Discussion
<i>Step 6: Ensure use and share lessons learned</i>	<ul style="list-style-type: none"> -Poster presentations at national meetings -Dissertation Defense -Distribution of findings to study participants -Publication in academic journals
Standards for Effective Evaluation	
<i>Utility:</i>	<ul style="list-style-type: none"> - The need exists for an objective, formal program evaluation of the decision to add Krabbe disease screening to the NYS newborn screening panel. -Krabbe disease was not recommended for addition to the core panel of conditions for newborn screening in 2009 due to lack of supporting evidence.
<i>Feasibility:</i>	<ul style="list-style-type: none"> -The timeline for data collection was estimated at 1 year. -Funding obtained from a grant awarded by Sigma Theta Tau – Alpha Zeta Chapter
<i>Propriety:</i>	<ul style="list-style-type: none"> -Investigator completed training in Human Subjects Research Protection -Study approved by the Columbia University Institutional Review Board -All participants signed informed consent prior to study participation.
<i>Accuracy:</i>	<ul style="list-style-type: none"> -All sources are documented. -Audit trail of data collection and analysis available.
Source: Adapted from Centers for Disease Control and Prevention, 1999	

Overview of Aims and Methods

A brief overview of the aims, analytic methods, and data sources is presented in Table 2. This is followed by the detailed descriptions of the methodology for each aim.

Table 2
Design and Methods of Krabbe Disease Program Evaluation

Study Aim	Method	Data Sources
Stakeholder perceptions of the Krabbe Disease screening program in New York State.	Qualitative thematic analysis to analyze interviews of each stakeholder group	<ul style="list-style-type: none"> • Semi-structured interviews using interview guides based on programmatic goals • State laboratory officials • Medical directors of designated Specialized care centers • Representative of Hunter's Hope Parent Advocacy group • Parents of infants who screened positive for Krabbe disease
Assess the Krabbe disease test characteristics with the most recent data available.	Calculate sensitivity, specificity, positive predictive value, negative predictive value, and prevalence	<ul style="list-style-type: none"> • Public records of test results from August 2006-July 2010 • Krabbe Consortium meeting minutes • Director of confirmatory testing laboratory
Assess the actual costs of the Krabbe disease screening program.	Cost identification analysis to calculate the cost of Krabbe disease screening from the perspective of the State	<ul style="list-style-type: none"> • Cost and charge data from confirmatory testing laboratory • Cost and charge data from selected specialized care centers • Cost information from Wadsworth Laboratory • Calculated test characteristics from Aim 2

Data Collection and Analysis - Aim 1

To assess stakeholder perceptions of the Krabbe Disease screening program in New York State.

Data collection sites.

Data were collected from several sites in New York State. The sites included the Wadsworth Laboratory in the Department of Public Health located in Albany, NY, which is the laboratory that performs the newborn screening for the entire state. Medical stakeholders at all eight specialized care centers for inherited metabolic disease located across New York State were contacted. These specialized care centers are designated under Article 28 of the Public Health Law§2500-a as health care facilities that can provide treatment and/or services to children identified by the newborn screening laboratory (New York State Newborn Screening Implementation Task Force, 2003). Finally, data were also collected from the Lysosomal Disease Testing Laboratory at Jefferson University in Philadelphia, Pennsylvania, which performs the confirmatory testing for the infants that screen positive for KD.

Sample description.

The sample selection for each stakeholder group was purposive, using a criterion strategy described by Miles and Huberman (1994). This strategy includes selecting participants who had a specific role in the criterion under study and is one technique used to ensure transferability of results. Purposive sampling was used to choose participants who had experience within the KD screening program. Using the CDC Framework as a guide, purposive sampling was an appropriate choice given that participants are members

of specific stakeholder groups, which is the criterion for participation. Table 3 provides a description of the total population available for this study for each stakeholder group.

Table 3

Sample Description Table

Stakeholder group	Description	Total population
Those involved in program operations	Governor of New York State	1
	Commissioner of Public Health	1
	Director of newborn screening program	1
Those in a position to make decisions about the program	Director of Wadsworth Laboratory	1
	Director of Metabolic Disorders	1
	Director of Confirmatory Testing Laboratory	1
	Medical directors and neurologists at the Metabolic Centers of Excellence	11
	Nurse practitioners/genetic counselors	5
Those served or affected by the program	Representative of Hunter's Hope parent advocacy group	1
	Parents of infants screened positive for Krabbe disease meeting inclusion criteria	154
Total		177

The largest population of the stakeholders is represented by the parents of infants who have screened positive for KD since inception of the program. As of July 2010, 185 infants screened positive and were referred for confirmatory enzyme testing (Duffner, 2010). It was not feasible or necessary to interview parents of all infants who screened positive, so the following inclusion criteria were developed for participation in this study: 1) ability to speak and understand English, 2) willingness to provide informed consent

prior to the interview, and 3) willingness to allow audio recording of the interview. After these criteria were applied, a total of 154 parent stakeholders were identified for recruitment and total of 23 medical, legislative, and program director stakeholders were identified.

Recruitment and retention.

To engage the stakeholder groups in study participation, a short abstract was developed describing the aims and significance of the proposed research and provided to the identified stakeholders (see Appendix 4). Parents of infants who screened positive for KD received this information from their evaluating specialized care center. Those interested in study participation returned a stamped, pre-addressed postcard to the investigator. Following receipt of the postcard, the investigator contacted the parent to schedule an interview. Medical personnel were contacted directly by the investigator. Recruitment was planned until thematic saturation was achieved. Generally, this occurs following completion of 10 to 15 interviews (Strauss & Corbin, 1998).

Interview guides.

Based on the synthesized description and programmatic goals, initial interview guides for each of the stakeholder groups were developed (Appendix 5). Guides varied slightly depending on the program goals and descriptions for each of the stakeholder groups. To assess for bias and content, the dissertation advisor evaluated the interview guides prior to use. These guides provided a framework for the investigator, but were neither rigid nor inclusive. The semi-structured format allowed flexibility, and the guides changed over the course of the study, with questions being added or discarded as the

interviews progressed, using the process of constant iteration. This process is described by Creswell (1998), as a zigzag, consisting of gathering data, analyzing data, and then returning to the field to collect new information using the previous data to guide the collection. The guides used in the last interviews are found in Appendix 6.

Interview procedure.

The student investigator conducted face to face interviews with medical participants at six of the eight specialized care centers, the Wadsworth Laboratory, and the confirmatory testing laboratory in Philadelphia, PA. Parent participant interviews were conducted in their homes or other location of their choice. Four interviews were conducted by telephone for participant convenience.

All interviews were audio recorded using a digital recording device. A back-up device was available in case of device failure. Field notes were taken during the interview to add context and clarity to the subsequent transcriptions. Interviews lasted approximately one hour.

Human subjects protection.

Aim 1 was the only aim that required active human subject participation. The Columbia University Medical Center Institutional Review Board approved all study procedures (see Appendix 4 for copy of IRB certificate and stamped informed consent). All participants provided signed informed consent prior to being interviewed.

Data analysis - Aim 1.

The qualitative method of emergent content analysis was used to analyze the data. This method has been described as an inductive approach allowing categories and themes

to emerge from the data to better understand how stakeholders perceive the process under study (Hsieh & Shannon, 2005). This is an iterative process, consisting of six steps described by Johnson and LaMontagne (1993). These steps are: 1) Preparation of the data, including transcription of the audiotaped interviews; 2) thorough familiarity of the data through multiple readings of the transcripts and by listening carefully to the taped interviews; 3) identification of units of analysis by bracketing; 4) initial designation of codes; 5) refinement of codes into categories; and 6) establishing major contextual themes from the categories. By adhering to an analytic process, the validity and trustworthiness of the study is increased (Hsieh & Shannon, 2005). In this section, examples are provided for each of the steps of this process.

To prepare the data, after each interview was completed, the recorded interviews were transcribed by a transcriptionist and reviewed for accuracy by the investigator. All interview recordings and transcripts were assigned initials and numbers to assure participant confidentiality. The following initials were assigned to each participant category: Program directors (D), medical personnel (M), and parents (P). Numbers were assigned sequentially, in the order of the interviews.

Based on work done by Barbour, et al. (2000) each one-hour interview was predicted to take 2 to 4 hours to transcribe and an additional 20 hours to analyze. Transcripts and field notes were managed using the NVIVO 8® (2008) qualitative research software program, which also provided an audit trail as the qualitative analysis progressed.

Units of analysis were defined as the interview text. Beginning with the first

interview, every transcript was reviewed, and initial codes were assigned to the interview text, identifying topics and phenomena of interest. Transcripts were reviewed in an ongoing fashion to uncover similarities, focusing on the manifest content of the interviews using a constant comparative approach. Manifest content is defined as the visible, obvious components of what is said (Graneheim & Lundman, 2004). This basic coding process is a method used to organize large quantities of text into much fewer categories that describe the content of what is being said (Weber, 1990). This was done by reading each transcript in entirety, then rereading and highlighting text and phrases that captured the meaning of what the participant was saying. A code was assigned to this highlighted text by the investigator. After two interviews had been coded, these codes were used to identify similar text and phrases in the following interview texts, adding new codes when data did not fit into any of the existing codes. This continued throughout the data collection process.

To refine the codes into categories, the transcripts were reviewed again, beginning with the third interview, and codes were grouped as similarities were identified. The categories served to illustrate the stakeholders' understanding of KD testing relating to both the program goals and their experience of the process. Categories were reviewed and revised throughout the process of data collection, and some categories were eliminated, as the codes were found to fit better in other categories.

Constant comparative analysis of the data between interviews, that is, comparing the content of each interview to the others (Glasser & Strauss, 1967), was conducted to group the categories into themes. Themes represent overarching concepts found within

the categories (Miles & Huberman, 1994) and a definition of the theme was developed to capture the overarching concept. The technique of constant comparative analysis also aids in the assessment of theoretical saturation, the point at which collecting data yields no new information (Strauss & Corbin, 1998, p.136).

Data Collection and Analysis - Aim 2

Assess the KD test characteristics with the most recent data available.

The data sources for Aim 2 were the newborn screening results of New York State collected from August 2006 until July 2010. These publicly available annual reports included those infants who screened positive for KD and those with no disease, and are found on the Wadsworth Center website (Wadsworth Laboratory, 2009). Confirmatory test results and disposition of children with positive results were obtained from the meeting minutes of the Krabbe Consortium (Duffner, 2010).

Test characteristics assessed for Aim 2 were sensitivity, specificity, positive predictive value and negative predictive value. These characteristics are commonly used to evaluate the performance of a screening test (Sahai & Marsden, 2009). Sensitivity is defined as the probability of a positive test given the presence of the target disease. Specificity is defined as the proportion of patients who do not have the target disease and who screened negative (Strauss, Richardson, Glasziou, & Haynes, 2005). The positive predictive value represents the precision of the test, in other words, the likelihood that a patient with a positive screen actually has KD. The negative predictive value represents the accuracy of the test, or whether the initial screening test correctly identifies those infants who do not have KD (Greenberg, Daniels, Flanders, Eley, & Boring III, 2006).

Prevalence was also calculated and describes the number of people with a disease in a given population within a specified time frame. Table 4 is the contingency table representing the calculations used.

Table 4
Contingency table to assess KD test characteristics

Newborn Screen (DBS)		Krabbe Confirmatory Testing (GALC enzyme)		
		At Risk	No Risk	Totals
Screening test result	Positive screen	True Positive a	False Positive b	a + b
	Negative screen	False Negative c	True Negative d	c + d
Totals		a + c	b + d	a + b + c + d

Note: DBS – dried blood spot
 GALC - galactocerebrocidase
 Sensitivity = $a / (a + c)$
 Specificity = $d / (d + b)$
 Positive Predictive value = $a / (a + b)$
 Negative Predictive value = $d / (c + d)$
 Prevalence = $(a+c) / (a+b+c+d)$

In the case of KD, newborn screen results from the dried blood spots and confirmatory enzyme results from a venipuncture are not represented in the same units of measurement. Table 5 provides the units of measurement for both positive and negative test newborn screening results and confirmatory enzyme results presented in the same format as the contingency table used to calculate results.

Table 5
Krabbe disease testing defining characteristics

Newborn Screen Testing Anylate: % Daily Mean Activity of (GALC)	Krabbe Confirmatory Testing	
Positive Screen ≤12% activity + mutations	High Risk (present) GALC ≤0.15 nmol/hr/mg protein + mutations	No Risk (negative) GALC > 0.16 nmol/hr/mg protein (may have mutations)
Negative Screen > 12% activity	False Negative (later develop KD)	True Negative (never develop KD)

Note: GALC – galactocerebrocidase
 KD – Krabbe disease

In newborn screening, it would be ideal to have a test with a sensitivity, specificity, and positive predictive value of 100% and a false positive rate of 0 (Sahai & Marsden, 2009). For the disorders on newborn screening panels, the cut-off points for reporting are set high in an attempt to eliminate false negative results, with the understanding there will be many false positive screens. To compensate for the expected number of false positives, the confirmatory test for the disorder should have a high positive predictive value to assure prompt treatment initiation, and avert morbidity or mortality. Since the positive predictive value is affected by the prevalence of a disorder, and all the disorders on newborn screening panels are rare, the expected positive predictive value ranges from 10-20% (2009).

Collection and Analysis - Aim 3

Assess the actual costs of the Krabbe disease screening program.

A simple cost analysis was conducted using the costs associated with the KD screening program. This type of analysis measures the cost of a program, and was chosen because there were no published data regarding the costs associated with KD screening; confirmatory testing, neurologic consultation and neurodiagnostic work up.

To obtain a range of estimates, cost and charge data were collected from a variety of sources, including: the New York State Medicaid Physician Fee Schedule 2010 (New York State Department of Health, 2010), Mount Sinai Charges (Mount Sinai Medical Center, 2010), United Health Care Consumer Cost data (United health care treatment cost estimator, 2011), and Strong Memorial Hospital costs from Rochester, NY (Kwon, 2007). These sources were chosen to represent urban areas, rural areas, insured and uninsured financial data.

The cost categories displayed in Table 6 represent the office visits and procedures infants undergo after a positive newborn screen for KD and after a positive confirmatory enzyme test based on the consensus protocol used in New York State (Duffner et al., 2009). The cost categories are displayed using the Current Procedure Terminology II (CPT II®) codes (American Medical Association, 2009) used for billing and the International Statistical Classification of Diseases (ICD-9) codes (International statistical classification of diseases, 1977) used for designation of the diagnosis to justify the charges.

Table 6:
Cost Categories

	Name of Service	CPT Code	ICD-9 Code
Positive newborn screen for Krabbe disease	New patient consult (Metabolic)	99205	796.6
	Venipuncture < 3 yrs	36400	796.6
	Confirmatory enzyme test	82657	796.6
Infants with positive confirmatory enzyme test	New patient consult (Neurology)	99205	330
	Lumbar puncture & analysis (inpatient)	62270	330
	Nerve conduction velocity w/F-wave	95903	330
	Brainstem auditory evoked response	92585	330
	MRI Brain w/wo contrast	70553	330
	Hospital admission – pediatric	99357	330
	Anesthesia for MRI	99148	330

Note: 796.6 – Abnormal Findings on Newborn Screen
330 – Leukodystrophy-NOS

Every effort was made to use cost-accounting data instead of actual charges to reflect a more realistic reporting of the costs involved with the procedures in this study. Those costs that were reported in another year's currency were converted to 2010 US dollars by using the cost conversion factor calculator found on the Bureau of Labor Statistics web page (www.bls.gov/guide/geography/inflation.htm). This calculator included geographic variation specific to New York State. Charge data from Mount Sinai Medical Center were converted to costs using the typical hospital cost to charge ratio conversion of 0.39 (Medi-cost.com, 2011).

The analysis was conducted from the perspective of the State. The time horizon

for cost data was from the time of initial blood collection in the newborn nursery to the time of neurologic evaluation and neurodiagnostic workup for a positive confirmatory enzyme test. Using the protocol established by the Krabbe Consortium of New York, this horizon is 2 weeks. Because of the short time frame, discounting is not applicable. The total cost of the program was then calculated for the period of time from August 2006 through July 2010 based on the total number of positive results from Aim 2. The analysis was based on best point estimates available.

Assumptions made in this analysis are that all newborn screening is performed according to the written protocol from the Wadsworth Laboratory and confirmatory testing and procedures are performed according to the written protocol developed by the Krabbe Disease Consortium (Appendix 2). There is no distinction made between the infants with early infantile Krabbe disease and the group of infants with very low enzyme activity and mutations consistent with later onset Krabbe disease after confirmatory testing. The rationale for this decision is that both groups initially undergo the same procedures as outlined in Table 6.

Only direct medical care costs were included in this analysis. Direct nonmedical costs such as parent absence from work and travel time were included in probing questioning during the qualitative interviews. However, the formal cost identification analysis did not include these costs. Other indirect costs, such as staff time and postage fees were also not included in this analysis.

Chapter IV: Results

In this chapter, the results of the study are presented in detail for each of the three study aims. Each aim will be repeated for the reader's convenience.

Aim 1

To assess stakeholder perceptions of the Krabbe Disease screening program in New York State.

To gain the perspective of stakeholders regarding the addition of KD screening to the newborn screening panel, a total of 22 in-depth interviews were conducted. After informed consent was signed, 18 interviews were conducted face-to-face and four were conducted by telephone. For this study, theoretical saturation was achieved after 20 interviews, two more interviews were conducted to confirm this, and then recruitment was halted.

Attempts were made by the investigator to contact Governor Pataki and Commissioner of Health, Kenneth Pass, as legislative representatives, however, neither responded to the invitation to participate. Two of the metabolic specialty center directors were not available to participate. The specialty center directors mailed a total of 51 invitations to parents, of which nine responded. One participant was a parent advocate and the remaining 12 participants had various medical backgrounds and were involved in the operation of the program. Table 7 displays these participants and includes the total population of each stakeholder group and the actual sample size.

Table 7:
Study Participant Description

Stakeholder Group	Description	Total Population	Actual Sample
Those involved in program operations	Governor of New York	1	0
	Commissioner of Public Health	1	0
	Director of newborn screening program	1	1
	Director of Wadsworth Lab	1	1
	Director of Metabolic Disorders	1	0
	Director of Confirmatory Testing Laboratory	1	1
Those in a position to make decisions about the program	Medical directors and neurologists at the Metabolic Specialty Centers	11	8
	Nurse practitioners/genetic counselors	5	1
	Representative of Hunter's Hope parent advocacy group	1	1
Those served or affected by the program	Parents of infants screened positive for Krabbe disease	154	9
Totals		177	22

Coding analysis.

From the thick, rich descriptions of participant experiences with the Krabbe disease program, 65 initial codes were assigned to the text of the interview transcripts. These preliminary codes served to describe initial findings in the data, and to discover emerging similarities or areas of interest meriting further exploration in future interviews.

Each code was then reviewed by the investigator and her sponsor and placed in

eight categories. These categories reflected relationships and patterns found in the coded data. Once categories were established, further review of the data revealed similarities, resulting in elimination of two categories and creation of final themes. Themes represent the overarching concept that is found throughout the categories. Morse (2008) describes a theme as, “the meaningful essence that runs throughout the data,” (p.727).

Table 8 displays the initial codes, categories, revisions, and final themes, as well as the percentage of contribution to each theme by parent and medical participants. For example, codes found in the *Information Needs* category, such as *Advice, Parent Education, and Clarity of Information* reflected the ongoing process of *Communication*, and were merged into that theme. The category *Treatment* was eliminated, as the codes in this category described other phenomena. The code *Challenges to Krabbe screening* was moved from the category *Treatment Issues* to the theme *Unintended Consequences*, with the rationale that challenges to Krabbe screening were not desired outcomes of the program, and were moved to the theme that captured this concept.

There were also codes initially assigned to one theme, but after further analysis, were found to better represent something else. For example, *Treatment Issues* and *Erring on the side of caution* were initially coded as examples of the emerging *Knowledge and Science* concerning KD. However, after several interviews, and using constant comparison, it became evident that this knowledge presented dilemmas for the medical participants. Therefore, those codes were moved to the theme *Moral Issues*.

Table 8: *Coding Matrix*

Initial Codes	Categories	Refinement	Themes
Lack of knowledge:KD Comparing to other disorders ID of at risk infants Rationale for adding to NBS Statistics What we don't know Multi-state cooperative Technical Issues Defining risk categories	Science & Knowledge	<i>Moved to Moral Issues:</i> Testing as research Results as gray area Erring on the side of caution Testing as Research	Science & Knowledge Parents = 6% Medical = 94%
Unintended consequences Stressed out Physical reaction to notification Opening a Pandora's box Misleading information Harboring latent fear Damage control Despair Burden-time	Unintended Consequences	<i>Added:</i> Challenges to Krabbe screening Vulnerability <i>Removed:</i> Cost	Unintended Consequences Parents = 63% Medical = 37%
Concerns not heard Confirmatory protocol Consistency Follow up Provider information	Communication	<i>Added:</i> Information Needs, Supporting parents	Communication Parents = 66% Medical = 34%

Initial Codes	Categories	Refinement	Themes
Urgency Treatment Issues Supporting parents	Erring on the side of caution Challenges to Krabbe screening Vulnerability Treatment	<i>Eliminated this category</i>	
Compelled to test NBS as political NBS as important Parental refusal	Legislative Mandate No plan in place Benefit of screening Trusting professionals Legislative/Political	<i>Added:</i> Urgency Cost	Legislative/Political Parents = 33% Medical = 67%
Advice Parent Education Searching for Information	Clarity of information Provider Education Incorrect information Information Needs	<i>Eliminated this category</i> All codes merged into Communication	
Who decides what info to give Results as gray area Erring on the side of caution Screening for adult disease Notification as coercion		<i>Added:</i> Treatment Issues Testing as research Results as gray area Erring on the side of caution Testing as Research	Moral Issues Parents = 0 Medical = 100%

The five final themes that emerged were *Legislative/Political*, *Unintended Consequences*, *Knowledge and Science*, *Communication*, and *Moral Issues*. Each theme is discussed in detail with exemplar quotes provided in the following sections.

Theme: Legislative/Political.

In New York State, the Public Health Law §2500-a grants the Commissioner of Health the authority to add conditions to the newborn screening panel by regulation (Expansion of the New York State newborn screening panel, 2006). This is an example of legislation; the action of making or changing laws. The addition of KD was legislative, however, the process that brought the issue to the attention of legislators was political. The term politics is defined by Mason, et al. (2007), as the process of influencing the allocation of resources structure or affairs of the government.

Both medical and parent participants spoke about the politics surrounding the legislation leading to the addition of KD to the screening panel. Medical participants contributed 67% of the content of this theme, while parents contributed 33% of the content. The *Legislative/Political* theme includes comments regarding not only the political process involved, but also the concept of being mandated to test.

Patient advocacy groups have been influential in the establishment and expansion of newborn screening (Clayton, 2010; Paul, 2008). These advocacy groups are comprised of parents with affected children and exert voting power, and political contributions. The mission of advocacy groups is often singular, as expressed by this medical participant:

I mean this was basically a parent of a child, who I'm sure was well-versed in the

details of the condition. But again, granted, not a public policy person by any means, going to a governor, and I don't think Governor Pataki had any extensive background in neurology or genetics and basically, both of them deciding this is what needs to be done. You know, it just seemed like for a lot of the directors that that was a little bit strange to be making the decision with such far-reaching implications without even having a discussion. (M02)

Considering that decisions regarding inclusion of new conditions to the newborn screening panel in New York State must serve the goal of preserving public health (Expansion of the New York State newborn screening panel, 2006), a condition must be recognized as a threat to the public. If there is little awareness of a condition, as there often is in rare diseases, no recognition of threat can exist. If awareness about a disease can be increased, perhaps more research toward treatment or a cure will occur. To this end, advocacy groups have used the political process to push inclusion of rare diseases in newborn screening, which in turn raises public awareness as infants screen positive. Even if no disease is confirmed after a positive newborn screen, families of these infants are now aware of the condition, the infants' pediatricians are now aware, and the disease may now be perceived as a threat. One participant describes this as a poor use of the political process:

What goes wrong with the newborn screens? ... the advocacy groups or the parents' groups and so on [recognize] that... there is not treatment and therefore we need this program to force the experts to recognize that there is a need for treatment, to force people to acknowledge how frequent the disorder is. (M03)

In addition to advocacy groups, pharmaceutical companies and other corporate entities that stand to profit financially from identifying diseases early may exert political influence. Medical participants expressed concern that the political process of lobbying carries more weight than available solid science. This concern is summarized by this participant:

Well, I think you can look at Krabbe and wonder what the driving force was. You know, these [screening tests] are not being physician driven. I think that they're being driven by consumers and/or biotech firms...and these advocate groups.
(M08)

Other participants add that the scientific evidence to support addition of new disorders has been superseded by the political process. As one medical participant states:

...unfortunately, newborn screening has become imbued with politics, as I guess a lot of things are. And it's sort of drifted away from the kind of rigorous scientific goals that started it. (M02)

Medical participants questioned the ability of parents, legislators, and lobbyists to interpret available scientific evidence. There appeared to be incongruity between science and the political process. As the decision to add KD to the newborn screening panel advanced, the medical community questioned this action, but was not given an opportunity to adequately voice their concerns. One participant describes feeling unsafe, and ultimately deprived of the ability to protect patients from the potential consequences of adding Krabbe screening to the newborn panel:

So I think this was driven politically. It was driven by people who didn't ask the right questions, it was not politically safe, it was not safe to ask the right questions...and we as a special team failed to protect these lay people from themselves. (M07)

Another medical participant voiced a similar opinion, regarding the lack of discussion surrounding the implementation of the screening test into practice. When adding a new condition to the panel, the process of parent notification, reliable confirmatory testing, and adequate follow-up procedures for those infants who screen positive must also be considered. This participant acknowledges the lab test was available, but points out that in the case of KD testing, little input had been sought to figure out how the test would work in practice:

...although they had given good thought to the how do you do it in the lab in terms of the routine newborn screening and so on, it didn't seem to me that any thought had been given at all to how we were going to implement this in terms of what it meant when you had a positive screen. (M05)

The legislative mandate came as a surprise to the metabolic specialists. The political process was perceived to carry greater weight than the expert opinion of the physicians, who did not feel they were part of the decision making process. The idea that a condition was added seemingly without full appreciation of the newborn screening process or considering how results could impact families seemed to trouble the medical participants.

Parents described their understanding of the political process differently. It was assumed that because newborn screening was a law, there was a review process in place to determine the conditions to include. This assumption allowed parents to accept that Krabbe screening was necessary. Although the process was not well understood, this parent was certain the rationale to add conditions was valid.

... it's whatever the state legislature deems appropriate. They just don't add stuff willy-nilly, which I understand... somebody deemed it necessary. It got on somebody's radar somewhere to add this to the list of mandatory newborn screening tests. So I didn't really question the necessity of it. (P07)

Another parent acknowledged the political process and offered his perception of what may have influenced the inclusion of KD on the panel, "I mean like somebody's friends with some football player; his kid has this and now it's a law," (P01). While disagreeing with the political process, he also acknowledged the importance of newborn screening as a public health law. Begrudgingly, he commented about the importance of screening to those found to be affected in relation to his family's discomfort with the process:

...well that's kind of a dumb law. But it didn't hurt us as much as it probably helps the people that need to know that their kids had it. So it's really hard to be too upset about it. It's like getting a vaccine. If your kid is the one kid who reacts negatively to a vaccine, it's hard to be like - well we shouldn't get vaccines. You're just the lone guy that's out of luck. (P01)

While parent participants understood that the screening process was a law, and

also understood this testing was important for their infant, there were concerns regarding their options. The underlying mandate, the feeling of not having an option to refuse confirmatory testing contributed to these concerns. One parent recalls:

I was just kind of like, my God, we really have no choice about, you know, like this was something we were kind of pressed into, and we're handing over insurance cards, and you know, thank God we have good insurance. But, you know...I did have a moment where I was like, what am I getting myself into? Am I going to end up with some kind of, you know, massive financial responsibility? Which, you know, at that moment it's not the first concern, but it was alarming. (P03)

Other participants acknowledged this concern about financial obligation. One director comments not about the screening, but about what would happen to families who pursued treatment:

...now what this is going to do is for those kids that can't pay, they have families who can't pay? It's going to cost a fortune...either a quarter of a million or three hundred thousand for a transplant. (D03)

In summary, the *Legislative/Political* theme revealed that participants understood that newborn screening was a legislative mandate. They stated concern about politics having a greater influence in decision-making than expert interpretation of scientific evidence. Medical participants expressed their opinion that decisions were made based on availability of tests instead of consideration of the process involved in newborn

screening, and described their concerns were not heard. Interestingly, on page 9, paragraph 7 of the Emergency Rule legislation, the statement is made that, “There appears to be no potential for organized opposition.” However, the metabolic specialists, who would be impacted by this decision, expressed surprise about the mandate, and felt they were not provided the opportunity to oppose the decision.

Parents assumed the legislative process to add new tests to newborn screening was sound, and also understood the importance of screening for the population. However, the impression of not having an option in the process, and that financial obligations could become an issue remained concerns for parents and medical participants alike.

Theme: Unintended consequences.

The concept of unintended consequences refers to the actions of people, especially the government, having effects that are unanticipated or unplanned (Norton, 2008). These effects may be a positive unexpected benefit or a negative effect contrary to the original intention of the action. The theme *Unintended Consequences* includes positive effects that were unanticipated by those making the decision to add KD to the newborn screening panel, as well as negative issues that have emerged since the screening program began. In this theme, parent participants contributed 63% of the content and medical participants contributed 37%.

One positive benefit of adding KD to the newborn screening panel is the increased awareness of the disease by parents, their families and medical professionals. This increased awareness inspired one parent to continue to monitor for new information about KD:

So, you know, that's something that I would pay attention to, if there were something that came up about Krabbe disease where there were new findings, or just something you know, in the media that I had access to, I would pay close attention.(P03)

Another parent described that after learning more about KD, she recognized how the disease must affect other families. After the confirmatory testing revealed no risk to her child, her increased awareness led her to search for ways she could help families with children diagnosed with KD. This parent recalls:

I found a foundation ... that does research or something, and I know we initially made a donation right after, because we were so grateful that we weren't [affected], but we felt so sympathetic to a family that was going through something like this. (P08)

However, there were also unexpected negative consequences to adding KD to the screening panel. Physicians are aware that notifying parents of a positive newborn screen creates an emotional response, but they report being unprepared for the intensity of this response from parents where KD was concerned. Perhaps the response was due to the uncertainty about what the confirmatory results meant. Unlike the other disorders on the panel, with KD, "we were kind of unclear as to how to proceed, which babies would be high risk, which babies wouldn't be high risk," (M01). These medical participants reported their experiences with parent responses ranging from anxiety to denial to anger:

...many of them are so anxious after our initial conversation that they would

prefer to avoid us completely. (M01)

So I think we generate potentially this boogieman and I think parents sort that out by just sort of walking away from it. (M04)

...the first high risk family we got just was madder than hell. We were experimenting on a baby, why were we doing this? (M07)

Parents' comments confirmed the concerns of the medical participants. The intense emotional response following their notification of the screening results ranged from extreme reaction to physical in nature. This parent recalled:

I had a really hard time that time, I even went to the doctor and they gave me a lot of pills for depression and stuff like that... Well, I had trouble. I started hurting myself after that. It was a way to get the pain off of me, I guess, even though the pills weren't helping. (P05)

Another parent described her physical reaction stemming from the emotional response after being notified of the positive KD screen:

Yes and my milk went; it dried up and then I re-engorged and she couldn't latch on when I re-engorged because - I don't know why - because they were like huge rocks. And so, it didn't end up working out. I mean I don't know if that [the shock of being notified] would do that. I imagine it would because I was pretty sick. I couldn't eat. I thought she was going to die. (P02)

Another negative unintended consequence was the lingering feeling that their child would develop disease later in life. This latent fear may be a result of the risk categories defined by the Krabbe Consortium (Duffner et al., 2009) of high, moderate, or low risk to develop disease. Being told their child was at low or moderate risk to develop KD did not seem to provide sufficient reassurance that their child would not one day develop symptoms. Due to this uncertainty, parents reported a lack of confidence with the confirmatory test. The following parent comments describe this:

But to be honest, it was kind of hard to believe, because it seemed like such a scary thing in that there were so few false positives, that he was one in such a small number. It was something that I don't think we really quite trusted [the result] until maybe a year later. (P08)

...for the first six months of his life, any time he cried or if he didn't want to eat or if something was wrong, you know, not that I expect the worst and hope for the best, but I always did wonder in the back of my mind. What if they were wrong? (P07)

Medical participants' comments corroborated these parent concerns. Since confirmatory test results are delivered with an ambiguous placement into a risk category, versus a definitive diagnosis of disease, health care providers couldn't provide closure for some of the families. This lack of definitive diagnosis, the label of "at risk," fits into the concept described by Timmermans (2010) of "patients-in-waiting." The following medical participants affirm what parents described:

I think that is a very common feeling I get from the parents, that once you're identified as being at some category of risk, be it low or moderate, you just always feel like you have that category of risk. (M06)

I think all of us worry that we're burdening the family with - sort of labeling the kid as defective, and that is not the intent, but it's the end result (M03).

When KD was added to the panel, the State projected that those infants with early infantile onset disease would be transplanted and no further follow up would be required by the metabolic center. In practice, the unanticipated finding of infants with very low enzyme activity and no symptoms of KD has raised concern among the medical participants regarding how long to follow these infants. Boelens (2006), suggests that it remains important to follow those at risk to develop KD for the rest of their lives. One participant comments:

...you're already working with a very anxious parent and then it's difficult to know, now what do we do with these 15 kids, how long are they going to be followed, these moderate and low risk kids? (M08)

In summary, the theme *Unintended Consequences*, participants described positive and negative consequences of the KD screening program that were not foreseen in the legislative process. Participants described both positive and negative consequences. Unintended consequences represent areas that warrant further attention by decision makers and researchers to resolve the issues that have arisen since KD screening began.

Theme: Knowledge and science.

It was understood by all the participants that a legislative process preceded the addition of KD to the newborn screening panel and that State law mandated the testing. Yet, participants also perceived that there were unanswered questions about KD. The process of answering questions and contributing to the knowledge about KD is the basis of this theme.

Knowledge is defined by the Oxford English Dictionary (Soanes & Stevenson, 2008) as: (1) facts, information, and skills acquired by a person through experience or education; the theoretical or practical understanding of a subject, or (2) awareness or familiarity gained by experience of a fact or situation. The word science is derived from the Latin word *scientia*, or knowledge (Soanes & Stevenson, 2008). Science refers to the systematic acquisition of knowledge through observation and experimentation, with the purpose of seeking predictions about future events. Scientific knowledge is disseminated through peer review and verification of results strengthens the science. Overall, the theme *Knowledge and Science* includes content about what is known and not known about KD and how existing knowledge contributed to the disease being added to the newborn screening panel. Science is also included in this theme because this term describes the systematic acquisition of new knowledge gained since the screening program has begun, through both observation and research.

The medical participants and directors provided 94% of the content in this theme, while only 6% of the content was provided by parent participants. This discrepancy likely reflects the medical participants' comfort level with the science behind screening for any

disease.

Prior to adding KD to the panel, existing knowledge was used to develop the test methodology and to make the case for inclusion. What was known about the disease shaped the new program and scientific literature provided rationale for the estimated number of infants that would be referred annually for confirmatory testing and neurology consultations. One medical participant describes using existing knowledge to create a laboratory test that met the needs of a population screening test:

...it [the only available Krabbe test] was a multiplex mass spec assay for several lipid storage diseases, which was done on only a few patients. ...our task was to take that and see if we could make it practical and get reasonable results on a population on newborns using dried blood samples. ... [now]we get it done start to finish from the DNA extraction to calling out the results in about 10 hours.

(D01)

Once the Krabbe screening program was operational, the number of referrals was found to differ from estimates formulated from the existing literature. In other words, science (systematic observation) began to change the existing knowledge about KD. This does not apply only to Krabbe screening, but also to other diseases added to the newborn screening panel. Participants commented on this concept:

...whenever you start screening for something new, there are always surprises when things don't go according to the literature...you get an incidence, you get what's available from children who are diagnosed systematically. There are always differences. (D01)

...when you start screening, you were going to run into things you never saw before. (D03)

As a result of the ongoing systematic observation provided by screening, emerging science began to replace existing knowledge, particularly when considering the prevalence of KD. Before the program began, it was estimated that annually, there would be 25 positive screens referred for confirmatory testing, with 2 or 3 diagnosed with infantile Krabbe. The later onset forms of the disease were not included in projected referrals, since the exceedingly rare incidence of this form of the disease was supported in the literature. However, since screening began, there has been an average of 46 positive newborn screens annually and only 4 infants diagnosed with early infantile KD over four years. Surprisingly, there have been 19 infants (5 per year) with low enzyme activity, at high or moderate risk to develop a later onset form of the disease. Participants discussed this phenomenon as follows:

Again, before, they said 85% have infantile and 15% have adult onset. We're seeing, it looks as though a lot more have the adult onset. (M01)

... we were under the assumption when we started this at 80% of kids identified with really awful early onset, and they're not, it's 20% or something, and 80% are [later onset]. So, we learned something. (M03)

We've learned that Krabbe disease is either like 30 times more common than we

thought it was and maybe it doesn't look like Krabbe disease, or that there are lots of people walking around with two mutations. (M07)

This new knowledge, that the later onset forms of KD appear to be more common, reinforced the medical participants' assertion that the natural history of this disease was largely unknown. The lack of scientific knowledge contributed to the medical participants' objection to the inclusion of KD in the newborn screening panel. They expressed concern that without adequate understanding about these later onset forms of KD, counseling parents becomes difficult, as answers about age of symptom onset, severity of disease, prognosis or treatment cannot be provided with certainty. These concerns are described in the following quotes:

... we don't actually know that much about that [high] category of risk... we don't know about late onset disease. (M06)

...there is such wide variation with the later onset forms, that's the problem, so that you do have a cadre of kids...less than 3 [years of age]so rapidly deteriorating, but then you get others who have very minor problems. (M05)

Usually the families want to know a black and white answer. Is my kid in danger or is my kid not in danger? If my kid is not in danger, than why are you telling me that my kid is in danger? (M03)

Despite the physicians' complaints about lack of knowledge causing difficulty in

providing advice to parents, all agreed that the screening test has provided new knowledge. A medical participant expressed the addition of KD as, "...a real opportunity to expand knowledge of the disorder and the issues within the families and so forth."

(M04)

Many participants compared Krabbe to the other metabolic disorders on the current newborn screening panel where the natural history and biology of the disorder is well known. The treatments for the other disorders are either effective, or the limitations of treatment are well known. By using comparison to other disorders, medical participants were able to describe how incomplete knowledge increased their discomfort regarding interaction with families. This discomfort is summarized in these participants' comments:

With sickle cell disease, it's easy, you have to point out change in the DNA when you have sickle cell disease or you don't. For this[Krabbe], you know, how do I explain to a parent that this one polymorphism knocks the enzyme down by 10%, and this one knocks it down 30%? (M03)

And frankly, if we are a little bit too aggressive with a kid with PKU, we can quickly correct it because we see them frequently and we monitor them. If we're a little too aggressive with a baby who might not have Krabbe disease and they end up going for transplantation and they end up with complications for the transplant, there's a lot more risks to that than there are risks to the others [disorders on the newborn screen]. (M01)

Other medical participants argued that without initiating screening, the new information about incidence of later onset KD would not have been known, and furthermore, there could never be a gain in knowledge without data gathered as a result of screening. The State mandated the addition of KD to the newborn panel based on best available evidence, and as illustrated in the following quotes, screening the newborn population for the disease provides information that would otherwise never have been known. These participants comment:

It's almost like a catch-22 argument because you're not going to know until you do it, but people think you shouldn't do it until you know, and it's as if we've practiced medicine that way. No medicine is practiced that way. ...we'll do it, and then they report their data, years down the road somebody does an evidence review, and makes an assertion... But, you've got to do that [initiate screening] to accumulate any evidence to sway one way or another, because there is no evidence in the beginning. (D01)

... [Krabbe screening is] analogous to doing sort of a broad population-based research program project. Because the act of doing the newborn screening was itself going to answer questions that we didn't know about the condition. And that we actually couldn't answer very well until you did start the newborn screening. (M02)

Medical participants were concerned about the impact of the test results on parents given their ability to counsel parents based on the paucity of scientific

knowledge. However, parents seemed to understand that KD was a new addition to the screening panel. Their comments indicate that because of this novelty, the physicians may not know everything about the disease. Two parents commented on the novelty of the test:

I guess I understood [that this test was new] based on the fact that this is not a disease that's terribly well understood. (P02)

...they only had two examples to show as far as success rate [of the test] was concerned, because up to that point, they didn't really know what they were dealing with, I guess, was the impression I got. (P06)

Parents described their new knowledge about KD differently than the medical participants. Instead of being concerned about what was not known about the disease, all parent participants expressed the idea that knowing their child carried a gene KD was important. One parent described this gain in knowledge in the context of considering what may have occurred if her baby had KD:

... to know one way or the other was really important to us, and when I found out what it [Krabbe disease] was and how quickly it hit, that knowing part would be so vital because the amount of time that you would have is so short, and whatever plans you have to make in terms of care and how to deal with the disease would have to be made so quickly. (P08)

Another parent offered her opinion regarding screening for KD, and the belief that the State should screen for more, not less disorders:

I think that's a good idea that they do screen for Krabbe because I would never believe my child could have Krabbe, it's beyond thinkable. I would think...they should screen for any of that kind of disease in every state, not only New York State, all throughout the states. (P05)

In summary, medical participants discussed KD as something they knew little about and that by implementing screening, emerging knowledge is contributing to the scientific knowledge. Medical participants differ in their opinions about whether the addition of this disease to the newborn screening panel was premature, citing the lack of knowledge about natural history, variability of symptom onset and severity, and the resulting inability to provide a concrete prognosis. Others argue that without initiating screening, new knowledge, such as the surprising finding that later onset forms of KD may be more common than the literature had supported, or that low enzyme activity may not result in symptoms would never be known. However, this new knowledge reinforces the premise that insufficient scientific knowledge demands further research about the disease. Medical participants express being comfortable with the other disorders on the panel because the biology of the disorder and limitations of treatment are well known.

When parents described their knowledge about KD being part of the newborn screen, there seemed to be an understanding that this was a new addition to the panel and that it was important to know whether their new baby had this disease. Parents were generally supportive of KD screening, and satisfied they knew important information about their child's health. In this way, the KD screening program appears to be meeting the goal set for parents, "To help insure your baby will be as healthy as possible." (New

York State Department of Health, 2006b, para 1).

Theme: Communication.

Information about KD is transferred using the complex process of communication. A simple description of this process is that information is sent and received. The transfer of information may include actions that confer knowledge and experiences, give advice and commands, ask questions, or seek information. All of these actions are a part of the newborn screening process. Furthermore, communication may be effective or ineffective. In effective communication, the intended recipient understands the information being sent as the sender intended the message to be understood. Ineffective communication implies the recipient does not understand the intended message. While knowledge about KD can contribute to the message, communication focuses on how that message is being sent.

The theme of Communication includes the activities surrounding the transfer of information about KD from person to person with the intent of sending a message. This transfer may be effective or ineffective, and may include not only face-to-face communication, but also the transfer of information from other sources, including the internet.

All the study participants discussed various communication activities, however, differences between medical personnel and parents were observed. All of the parents spoke at length about the communication process; how they were notified about the test results, what information medical professionals provided, where they found information, and their feelings surrounding this communication, contributing 66% of the content. For

parents, this theme was multifactorial. For physicians, their comments centered on concerns they had about trying to provide useful information to parents, and contributed 37% of the content to this theme.

The entire process of newborn screening begins with parents understanding their infant is receiving screening, as well as what the infant is being screened for. To address this, some states require parental informed consent prior to collecting blood (US General Accounting Office, 2003, pp 22-23.). New York State does not require consent for newborn screening but hospitals or birth attendants are required to provide education about the screening test (Test for phenylketonuria and other diseases and conditions, 1997). This education is often provided using a pamphlet describing screening without any verbal notification prior to the test. Many parents commented that they were unaware their infant had been screened in the hospital. These parents commented:

... because we honestly didn't even know that this was something that happened; that there was any blood taken from the baby at the hospital, or that the state runs specific tests for specific things. (P08)

I don't think he was screened when I was in the hospital. I think it was out [of the hospital]. (P04)

...they didn't even tell me that they were screening for it. (P05)

Since they were unaware that a screening test had been performed, the initial notification of a positive result was confusing. Parents were eager to discuss their

experiences about the communication of their baby's screening result, several cited the opportunity to talk about this as their reason for participating in this study. The initial notification was often experienced as a traumatic event that came as a surprise. The way parents experienced the communication of a positive KD screen is described poignantly in the following comments:

Her old pediatrician, one of the doctors there, called at five o'clock on a Friday afternoon and told me that there's something seriously wrong with my daughter.
(P02)

...one of the scarier parts for me was getting a call from some hospital that I had no affiliation with and telling me that they had test results from my son and that I needed to come in immediately. (P08)

That was the worst part of this whole thing, was how I was notified...so the whole process was nerve-wracking only because of the way I was notified. It was like a baseball bat out of nowhere. (P07)

...it devastated me. I was in shock. All I remember is he said that he had Krabbe disease and it's pretty serious, he can die within a year and they need to get tested and stuff like that. (P05)

I was shocked when I got the call because I just never thought that it would

happen. (P03)

After this initial notification, some parent participants sought information from their pediatricians, only to learn that the pediatricians either had little information or none at all. This lack of information caused more anxiety for parents as expressed in the following comments:

And the doctor said, 'Unfortunately I've never heard of this before; it's the very last item that's on the list of screening tests that they do,' and, 'It's terrible that I don't have more information for you, but it is what it is ...' So, of course, you know my son is ten days old and you hear something that comes back off newborn screening, you immediately think the worst. And then with the doctor not having any information for me, other than somebody called them and let them know. (P07)

Our pediatrician got the report, like the CDC information, and he acknowledged it on our next visit, but he didn't, you know, have any specific information, and honestly, I think he didn't have any information. I think he ... was not terribly familiar with Krabbe disease and was relying on sort of the information that was given to him... (P03)

And the pediatrician in the local doctor's office had no information whatsoever to share with me at that time. (P06)

What occurred in this process was that several parents reported being unaware

their infant had been screened while in the hospital. When they received notification of a positive KD screen, they described shock and needed reassurance and information. Unfortunately, parents reported their pediatricians were unable to provide this. Without information available from their pediatricians, parents were left to seek information independently and did so from a readily available resource, the internet. Parents report their experiences searching for information about KD on the internet:

I mean I got more off the internet than what the doctors could tell me. (P02)

But beyond that, if you just Google Krabbe disease, you get more information that you don't want because it's all the terrible stuff. (P07)

... like WebMD. And what do I remember about it, just that it's a neurological disorder that is really bad news. (P01)

Medical participants were sensitive to the anxiety that parents could experience when notified of a positive screen and were aware that this was not always handled well. They acknowledged the way the initial positive result was communicated made a difference in the ongoing process of confirmatory testing and follow up. One participant commented:

I think that that's a very important point that the director or physician involved with that initial encounter plays a big role in that of course. ... So the presentation I think is as critical in the creation or not of anxiety levels in the family. (M02)

In addition to the communication of initial screening results, ongoing communication with parents was described as difficult because there was inadequate information about KD available to the medical participants. The lack of information about later onset forms of the disease, in addition to the known variability of onset and severity of symptoms left medical participants with little evidence to rely upon when counseling parents. Their ability to recommend follow up and provide reassurance was compromised due to this paucity of information. Providing advice to parents became problematic as discussed by the following medical participants:

So, you know that information is hard to give to a brand new family with a brand new baby, "You might have a horrible disease and we have a treatment that might end up with the child dying anyway," And it's a big decision to make [seeking treatment], but we don't have all that information [about effectiveness] yet. And I think that that's also very important to have when you're counseling a newborn family. (M01)

I think that part of what's tricky is that even when their confirmatory enzyme testing comes back as normal... we really think that they're unlikely to develop disease, that they're more likely to be carriers...I just think that those patients, because they are identified for follow-up...get a lot of confusing information about what their diagnosis is. (M06)

Parents also expressed that once informed about the screening result; there was little information available to them about KD. They were unable to find detailed

information about the disorder, what the confirmatory test results meant, or about prognosis of KD. Compounding this lack of information about KD was the feeling that even the specialty centers were not able to provide them with sufficient answers to allay their fears. As a result, some parents described the feeling of being misled, as exemplified in this parent's comment:

I came in this like blank, I didn't know anything, and they wouldn't even tell me anything. They could just tell me like there's nothing to worry about. [But] They didn't tell me that, they said it could be a big issue. (P05)

Another parent described increased anxiety after her child's metabolic consultation:

So, I think the fact that I was just sort of...there was just this sort of lack of information... that it created more anxiety for me. (P03)

Other parents remained confused about their child's status resulting from incomplete or ambiguous information provided to them:

Ok, well, do we truly have nothing to worry about if [my baby] is just a carrier? What does "just a carrier" mean? (P07)

...he [the medical provider] gave me the rundown of what it is and then told me that he's not in the danger zone. He's not in the good zone. He's right in between, so he might not have anything happen to him. (P04)

The lack of trust, increased anxiety and continuing confusion described by parents may indicate the medical participants' described inability to provide thorough, concrete

information about KD. Medical participants were aware that their communication with parents was deficient. This is exemplified in the following comments:

I think parents recognize that there's something that's not being said, that there's something that doesn't make sense and that's not really clear. (M06)

[Physicians] are the ones who are running into issues with what do you tell, what does moderate or low risk mean? And as a parent, I would probably be concerned about that. (D02)

In conclusion, all participants acknowledged that communication is a difficult part of the KD screening program. Although educating parents about the newborn screen process is included in the public health law, most of the parents interviewed were unaware their infant had been screened in the nursery. Parents described distress over how they were notified of the results of their infant's newborn screen and medical participants acknowledged both the importance of this initial notification and the awareness this was not always presented well. Furthermore, meaningful, dependable information was found to be unavailable to both parents and medical participants, resulting in communication that engendered mistrust and misunderstanding.

Theme: Moral issues.

Morality is based on acceptance of certain accepted principles. In medicine, these principles are the values of Autonomy, Beneficence, Non-maleficence, Justice, Dignity and Honesty. Autonomy describes a patient's right to choose or refuse treatment. Beneficence means the provider will act in the best interest of the patient. Non-

malfeasance is often expressed as “first do no harm,” meaning the treatment should not harm the patient, or if it does, will provide a greater benefit than harm. Justice is based on the concept that treatments and access should be equally available to all. Dignity refers to the right of all persons to be treated with respect. Honesty is the provision of all the facts without censor (Beauchamp & Childress, 2001). The criteria for population health screening written by Wilson and Junger (1968) were based on these principles of medical practice. The theme of Moral Issues consists of comments representing conflicts of these moral principles described by participants surrounding the KD screening program. Medical participants contributed 100% of the content to this theme, perhaps reflecting that parents were unaware of any issues surrounding KD testing.

With the addition of KD to the newborn screening panel, a new precedent had emerged. Newborn screening could now include diseases that did not adhere to the Wilson and Junger (1968) criteria for screening. The opinion was that any disease could be added to the newborn screening panel if there was sufficient support, regardless of meeting the criteria for inclusion. One medical participant stated:

So again, it's just opened a Pandora's Box on many levels. It sort of gone against a lot of tenets of what newborn screening was sort of initially intended to do. That it sort of opened up a whole range of other competing interests to sort of get their foot in the door and say, "Why not do that disease then?" (M02)

Medical participants assert that the addition of KD to the newborn screening panel was premature because there was insufficient scientific knowledge about the disease. Where scientific knowledge is lacking, research is undertaken to contribute information

toward the understanding of a disease. Some of the medical participants contend that screening for KD is actually research, but because it is mandated by the State, families are not given the option to decline participation. The idea that research is being conducted on a vulnerable population without the opportunity for informed consent violates the principle of autonomy. This caused concern for some of the medical participants, as illustrated by these quotes:

... a lot of our treatment remains in this experimental research realm and that patients need to be protected by research protocols and consents. (M06)

So if the state didn't want to consent the patients early on then they at least needed to take responsibility for the fact that this was an experimental venture and that they are creating a population of children who can only be understood as research subjects. (M05)

Other medical participants argue that while screening for Krabbe may provide data that could be used for research, the screening is mandatory, and all newborns born in the state are receiving the same test. Because the test is mandated, everyone must comply with the law, including the physicians. There is no discrimination; everyone is participating equally, thus meeting the principle of justice. These participants describe their opinions about mandated research:

So while I may have philosophical disagreements with how it was all started, at this point, it's something that is done on every baby. And if a parent comes in and tells me that, "I don't want my baby to participate in research," well you know, it's

like the horse is out of the barn already because we've already gotten the test back. (M02)

...when they say it's," Oh, you're doing research". And, yes, I think a lot of this is research, but this is mandated. ... if this wasn't mandated we wouldn't be doing this. But since it is mandated and we're doing it, you kind of have to do the research. (M09)

The finding that infants are identified with very low enzyme activity but without the early infantile onset symptoms caused some of the medical participants to question if the State is adhering to the established guidelines for newborn screening. The very low enzyme activity may develop into a later onset form of KD; however, there is no predictive test that can provide that information, or it may never cause symptoms. Even if physicians were able give families a prognosis, only early infantile KD has a proven treatment (Escolar, Poe, Martin, & Kurtzberg, 2006; Friedman, 2008). By identifying a disorder that may not display symptoms until much later in the child's life, there is now a precedent for identification of adult onset diseases being added to the newborn screening panel. This precedent challenges the principles of honesty and non-maleficence. These medical participants described their concerns in the following comments:

There are two things that I think make this current process unethical. One is that we can't tell affected from unaffected, and the other is that we've done this [began screening for Krabbe disease] knowing we couldn't without getting consent for the screening. (M07)

So, in fact, have morphed...from a newborn screening program into a program that is screening infants for potentially adult onset, very variable diseases that are really hard to explain. (M01)

Another issue discussed by the medical participants was that the treatment for early infantile onset KD, UCBT, is associated with high morbidity and mortality (Friedman, 2008). The treatment may also be less effective than suggested in the original published research (Duffner, 2010; Friedman, 2008). The knowledge that the treatment is not as effective, and may cause further illness or death violates the principles of beneficence and non-maleficence, creating a dilemma among the medical participants. Many expressed concern that they are not offering families a cure, but rather a treatment of questionable efficacy. The medical participants commented:

What a huge commitment and a huge decision to decide to do a transplant on somebody and then it's not like you're going to do that and make them completely normal. (M08)

...you know, it[transplant] attenuates the disease, but it does not cure it, and that most...I don't know that all, but most of these children over time do seem to have a slow deterioration. (M05)

...the reason for the treatment was to be compassionate, yet nobody thinks about how compassionate it was to torture him in a hospital for a year and send him out

significantly impaired and only to get worse. (M07)

You know in Krabbe disease, so even if they survive the transplant, there are issues. We know that now, that they still have motor difficulties. (M02)

...we can promise them that their enzyme deficiency might be eliminated but we can't promise them a normal neurologic outcome. (M06)

In conclusion, medical participants were vocal about their moral conflicts surrounding KD screening. Some of the medical participants raised concerns about the moral challenges of screening for a disease that may not display symptoms until later in life, which challenges the principles of honesty and beneficence. Other medical participants described concern about conducting a form of research without full consent of everyone involved, violating the principle of autonomy. The legislative goal of adding KD to the newborn screening panel is to identify infants with serious but treatable medical conditions (Expansion of the New York State newborn screening panel, 2006). Medical participants were concerned that the treatment of KD, a UCBT, may not be as effective as initially reported, challenging the principle of beneficence and non-maleficence.

Summary.

From the emergent content analysis of stakeholder interviews and investigator field notes, five themes were identified: *Legislative/Political*, *Unintended Consequences*, *Knowledge and Science*, *Communication*, and *Moral Issues*. Stakeholder interviews

provided evidence to support that screening for KD at least partially meets the goals set by New York State.

All the stakeholder groups understood that KD screening was a legislative mandate. Parent participants concluded that legislators had sound reason to add KD to the panel, while medical participants expressed their opinions that emotional pleas from parent advocacy group agendas and financial support from lobbyists superseded scientific evidence.

Medical participants discussed the emotional reaction to the news of a positive KD screen was more intense than the other disorders on the newborn screening panel. Parent participant comments supported this assertion, revealing concerns about maternal health as an unintended consequence of screening for KD. Medical participants also worried that by placing an infant in a risk category, parents may be concerned about their child developing KD in the future. Parent participants did describe a latent fear of disease, but also described an increased awareness of KD and did not view this unintended consequence negatively.

Parent participants recalled their experiences surrounding communication of positive KD screening result. Although education about screening is required as part of the public health law, only one parent was aware that screening had been conducted in the nursery. Parents vividly recalled feelings of fear, stress, and in some cases, reacted with physical illness. In addition, parents reported that the information received from both their pediatricians and the metabolic specialty centers was insufficient, ambiguous, or incorrect.

Medical participants discussed the finding that newborn screening for KD was identifying infants with low enzyme activity and mutations found in persons with later onset forms of KD. They expressed concern about the lack of knowledge about the natural history of these later onset forms and discussed how this impacted their ability to effectively communicate risk to parents. They also discussed perception of moral dilemma regarding the treatment of KD and the concept of conducting research without parental consent.

Overall, parent participants expressed support for newborn screening, understood that it was mandated, and seemed to understand that KD was a new disease added to the screening panel. Parents were grateful they had information about their infant's health; however, it was unclear whether they understood what, if any significance the confirmatory results had for their infant. Medical participants perceived KD screening as premature, citing a lack of knowledge about the later onset forms of the disease that were being detected through newborn screening and concern about the risk and effectiveness of the UCBT for early infantile KD.

Aim 2

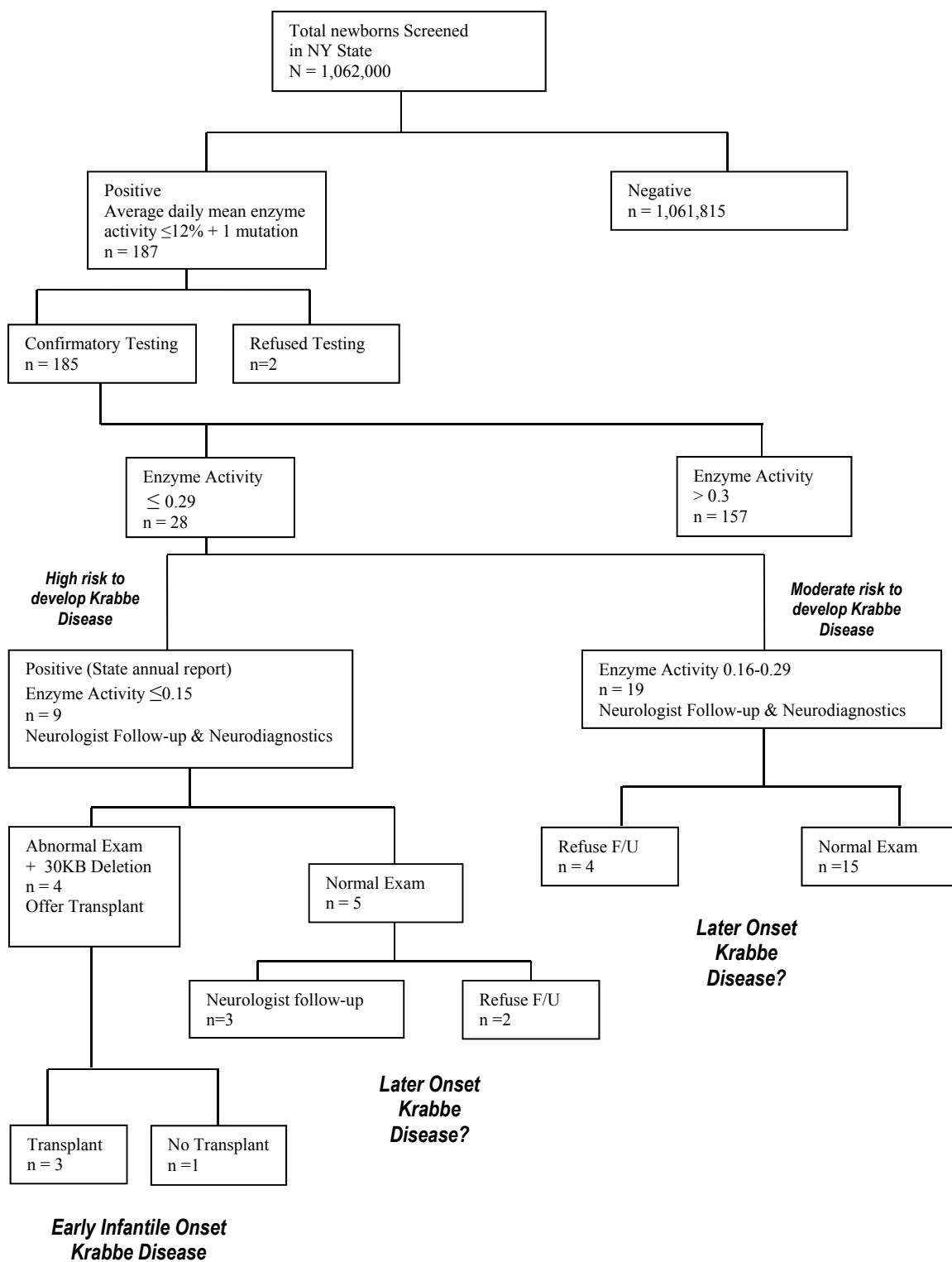
Assess the Krabbe disease test characteristics with the most recent data available.

New York State has published annual reports detailing all newborn screening results since 1990. These reports are available to the public on the Wadsworth Center website (Wadsworth Laboratory, 2009). Krabbe disease screening results have been included in the annual report since the program began in August of 2006. Confirmed cases are considered those infants determined to be at high risk to develop KD after

confirmatory enzyme testing at the Lysosomal Diseases Testing Laboratory in Philadelphia, Pennsylvania. This risk category includes all infants with galactocerebrocidase enzyme activity less than or equal to 0.15 nmol/h/mg protein (Duffner et al., 2009). Infants with enzyme activity 0.16 to 0.29 nmol/hr/mg protein are placed in a category of moderate risk to develop KD. Both the high risk and moderate risk infants are recommended to receive the same neurodiagnostic work up (MRI, LP, BAER, and NCV) and neurologic consultation. But infants in the moderate risk group are not reported as positive on the State annual reports.

As of July 2010, there were 1,062,000 infants screened. 187 infants were referred to a metabolic specialty center for positive Krabbe screening and to receive confirmatory enzyme testing. Two families declined to bring their child for confirmatory enzyme testing, and 185 infants were evaluated at one of the metabolic specialty centers. Of the 28 infants with positive confirmatory enzyme testing, 19 infants were categorized at moderate risk to develop KD, five infants were placed in the high risk category to develop KD, and 4 infants were diagnosed with early infantile KD. Figure 3 displays the breakdown of screening and confirmatory enzyme results.

Figure 3: New York State KD Screening Results August 2006 – July 2010



Data from the public annual reports (New York State Department of Health, 2006c, 2007, 2008, 2009) were used to populate the contingency table in order to calculate sensitivity, specificity, positive and negative predictive values, and prevalence of KD in New York State since August of 2006. (Table 9)

Table 9:
Contingency Table - State annual report

Newborn Screen test result	Krabbe Confirmatory Testing		Totals
	High Risk Present	No Risk Absent	
Positive screen	True Positive (a) 9	False Positive (b) 176	185
Negative screen	False Negative (c) 0	True Negative (d) 1,061,815	1,061,815
Totals	9	1,061,991	1,062,000

Note:

$$\text{Sensitivity} = a / (a + c) = 9 / 9 + 0 = 1.00 \times 100 = 100\%$$

$$\text{Specificity} = d / (d + b) = 1,061,815 / (1,061,815 + 176) = 0.99 \times 100 = 99\%$$

$$\text{Positive Predictive value} = a / (a + b) = 9 / (9 + 176) = 0.05 \times 100 = 5\%$$

$$\text{Neg. Predictive value} = d / (c + d) = 1,061,815 / (0 + 1,061,815) = 1.0 \times 100 = 100\%$$

$$\text{Prevalence} = 9 / 1,062,000 \times 100,000 = 0.85 / 100,000$$

All nine infants categorized as true positive for KD had enzyme activity ≤ 0.15 nmol/hr/mg protein and mutations of the GALC gene. Four were diagnosed with early infantile KD, and had the 30KB deletion associated with this form. Of these infants, three had undergone UCBT. One infant died during the transplant process, the other two infants are developmentally delayed, have severe gross motor delays, and are below the

third percentile for height and weight. One family opted not to pursue transplant and the infant deteriorated as expected. The remaining five infants in the true positive group are asymptomatic (Duffner, 2010).

However, it is important to note that the annual reports omit those infants who fall into the moderate risk group (GALC level $0.16 \leq 0.3$ nmol/hr/mg protein). Most of these infants have one or more mutations and several polymorphisms that are known to decrease enzyme activity. The Krabbe Disease Consortium has recommended neurologic evaluation every 3 months for the first and second years of life, including the battery of neurodiagnostic studies (Duffner, Caviness et al., 2009). As of July 2010, 19 infants fell into this category, but were excluded in the annual report. These data were obtained through the meeting minutes of the KD Consortium (Duffner, 2010). Table 10 presents these data to calculate test characteristics to include all children with low enzyme activity.

Table 10:
Contingency Table-including moderate risk infants

Newborn Screen test result	Krabbe Confirmatory Testing		Totals
	Present	Absent	
Positive screen	True Positive (a) 28	False Positive (b) 157	183
Negative screen	False Negative (c) 0	True Negative (d) 1,061,815	1,061,815
Totals	28	1,061,972	1,062,000

Note: Sensitivity = $a / (a + c) = 28 / (28+0) = 1.0 \times 100 = 100\%$

Specificity = $d / (d + b) = 1,061,815 / (157 + 1,061,815) = 0.99 \times 100 = 99\%$

Positive Predictive value = $a / (a + b) = 28 / (28 + 157) = 0.15 \times 100 = 15\%$

Negative Predictive value = $d / (c + d) = 1,061,815 / (0 + 1,061,815) = 1.0 \times 100 = 100\%$

Prevalence = $28 / 1,062,000 \times 100,000 = 2.6 / 100,000$ births

While inclusion of the infants at moderate risk for developing KD does not affect the sensitivity, specificity of the test, or negative predictive value, the positive predictive value rises from 5% to 15%. The KD prevalence rises from approximately 1/100,000 births to approximately 3/100,000 births. However, because KD is very rare, the positive predictive value will remain low. These results are typical of many disorders on the newborn screening panel. In the case of a disease like KD, negative predictive value, or the likelihood that a negative test indicates the infant will not develop disease is very important.

In the emergency rule legislation, the estimate was that 50 to 100 infants would be referred annually to metabolic specialty centers, with 95% of those infants ultimately not being diagnosed with KD (Expansion of the New York State newborn screening panel, 2006). For the period of August 2006 through July 2010, the total number of infants who had confirmatory testing was 185, or an average of 45 referrals annually. Using the estimate that 95% would not have KD, there should be two infants diagnosed in New York State annually. In practice, there have been only four infants diagnosed with early infantile KD since the screening program began (one per year). However, there have been five more infants identified with enzyme activity ≤ 0.15 nmol/hr/mg protein and

mutations that may indicate one of the later forms of KD. Inclusion of these infants would increase the number of infants with KD to two per year.

In addition, there have been 19 infants identified with enzyme activity <0.3 nmol/hr/mg protein and mutations that may cause a later form of KD. These infants are not reported as having KD in the annual report; however, their parents are told that their infant is at moderate risk to develop KD. These infants are scheduled for neurology consultation and neurodiagnostic testing, and the possibility that they may develop KD cannot be excluded. If these infants are included in the group of those diagnosed with KD, then there have been seven infants identified annually as a result of this program. If the possibility of later onset forms of KD cannot be excluded, then these infants should be reported as positive in the State Annual Report to accurately reflect actual practice.

Aim 3

Assess the actual costs of the Krabbe disease screening program.

Using data from Aim 2, 185 infants were referred to metabolic specialty centers for a positive KD newborn screen. These 185 infants all received confirmatory enzyme testing. Both parents had DNA analysis of the GALC gene and the infant's analysis was repeated. Table 11 represents the costs to Wadsworth Center associated with a positive KD screen and applies to all 185 infants. These costs are not billed to health insurance carriers.

Table 11:
Wadsworth Center Costs for Newborn Screen Positive Krabbe

Service	Cost
Repeat Screen and DNA analysis (infant and parents)	\$900
Confirmatory enzyme test	\$250
Total	\$1150

In addition, the cost of adding KD to the newborn screening panel was estimated at \$2.50 per infant screened (M. Caggana, personal communication, December 4, 2009). If this cost is applied to the 1,062,000 infants screened, the total is \$2,655,000.

Table 12 represents costs associated with the metabolic specialty center visit.

These costs are billed to the families, and are generally covered by insurance. For those families without insurance, Metabolic Centers may write off the cost associated with the initial confirmatory testing visit. The costs in Table 12 apply to the 185 infants who had positive newborn screens for KD.

Table 12:
Metabolic Center Costs for Newborn Screen Positive Krabbe

Service	Mount Sinai Charges	Mount Sinai Costs	Strong	Medicaid	United Health
New patient consult (Metabolic)	\$700	\$273	\$844	\$73	\$72
Venipuncture (infant and parents)	\$26	\$10	No data	\$24	0
Totals	\$726	\$283	\$844	\$97	\$72

Note:

Mount Sinai Medical Center costs-converted from charges using cost-to charge ratio
Strong Medical Center costs

Medicaid Reimbursement
United Health Reimbursement

The cost estimated for an infant with a positive newborn screen for KD ranges from \$72 to \$844, with an average cost of \$324 (SD = \$359). The Wadsworth Center cost was added, for a total average cost of \$1475 per infant with a positive Krabbe screen. When these costs are applied to the 185 infants referred to specialty metabolic centers, the total average cost for four years is \$272,875.

The 28 children with positive confirmatory screens, those with GALC enzyme levels <0.3 nmol/hr/mg protein, incurred additional costs displayed in Table 13. These costs are billed to parents and are covered by most insurance companies and Medicaid (New York State Department of Health, 2006a).

Table 13:
Direct costs for Confirmatory Test Positive for Krabbe Disease

Service	Mount Sinai Charges	Mount Sinai Costs	Strong	Medicaid	United Health
New patient consult (Neurology)	\$600	\$234	\$106	\$73	\$113
Lumbar Puncture	\$600	\$234	\$211	\$37	\$517
Nerve Conduction Velocity with F-wave	\$213	\$62	\$317	\$74	0
Brainstem Auditory Evoked Response	\$759	\$296	No data	\$101	\$50

MRI with and without contrast	\$2500	\$975	\$2103	\$597	\$475
Hospital admission - pediatric	\$3950	\$1540	in MRI cost	\$13	\$2166
Anesthesia for MRI	\$2800	\$1092	in MRI cost	\$26	\$300
Totals	\$12,558	\$3398	\$2737	\$921	\$3621

Note:

Mount Sinai Medical Center costs – converted from charges using cost-to-charge ratio
 Strong Medical Center costs
 Medicaid Reimbursement
 United Health Reimbursement

On average, it was estimated to cost \$2669 (SD = \$1224) per infant with a positive confirmatory result. Based on the source of the cost data, the range is \$921 to \$3621. For the 28 children with positive confirmatory enzyme results, the total estimated cost is \$74,732.

Over the time period from August 2006 through July 2010, the total cost of the program was estimated to cost an average of \$3,002,607. This translates into an annual average cost of \$750,652. For the fiscal year 2006-2007, New York State appropriated \$11 million to the total newborn screening program, an increase of \$2,000,000 from the previous year (Governor Pataki introduces 2006-07 executive budget, 2006). In addition, Title V block grant funding for 9 population-based services, including newborn screening totaled \$113,204,948 (McTague, B., 2009). The initial \$1150 is paid by the State to Wadsworth Center and is not billed to insurance. If the family has insurance, the cost of the metabolic consult and venipuncture will be reimbursed. If the family has no

insurance, or inadequate insurance, the metabolic center may absorb this cost (M. Wasserstein, personal communication, December 4, 2009). The metabolic centers receive no financial support from New York State (ASTHO, 2005), and the decision to absorb cost is up to the individual center. However, for those with positive confirmatory test results, the costs are not absorbed by the metabolic specialty center. This is not an issue for those families with Medicaid or insurance coverage, unless the policy has a high deductible or copay. As revealed in the qualitative interviews, cost was a concern for both the parents and the medical participants.

Chapter V: Discussion

In 2006, New York became the first state to add KD to the newborn screening panel. This study is the first formal systematic evaluation of the addition of KD to the New York State newborn screening panel and provides a comprehensive evaluation, including cost analysis, the input of stakeholder groups involved in the program, and assessment of test characteristics using the most recent data available. Specifically, using the CDC Framework for Program Evaluation in Public Health (Centers for Disease Control and Prevention, 1999), qualitative and quantitative methods were used to address the three aims. For Aim 1, the investigator interviewed 12 medical participants involved in making decisions about the program, and 10 parents who were directly affected by KD screening. Aim 2 involved gathering test result data from August 2006 through July 2010 to calculate sensitivity, specificity, positive and negative predictive value, and prevalence of KD. In Aim 3, cost and charge data were analyzed to determine cost of KD screening from the initial screening in the nursery to the time point of confirmatory neurodiagnostic testing from the perspective of the state. In this chapter, the findings from this study are discussed. This is followed by a discussion of the implications of the findings including recommendations for practice and policy and recommendations for future research. The strengths and limitations of this study are then discussed. Finally a dissemination plan provides details of how findings will be presented to inform decision-making for stakeholders in New York and other states.

Discussion of Findings

Aim 1.

Stakeholder interviews provided meaningful input regarding the KD screening program in operation. Using content analysis, five themes emerged from these interviews: *Legislative/Political*, *Unintended Consequences*, *Knowledge and Science*, *Communication*, and *Moral Issues*. Themes represent the common meaning found in all data included in that theme; however, the themes are interrelated. For example, information about KD is in the theme *Knowledge & Science*, however, when that information is given to another person, it becomes *Communication*.

Within the *Legislative/Political* theme, qualitative analysis of interview transcripts provided evidence that all parent participants in this study supported KD screening, and several indicated satisfaction in having more information about their child. Overall, parents believed screening was very important, and although they may have been stressed during the process, were grateful the program was in place and endorsed screening for as many diseases as possible. This finding is supported in the literature. In a cross-sectional study of 1322 prospective parents in the Netherlands, 73% of respondents supported newborn screening even for disorders that have no treatment (Plass, van El, Pieters, & Cornel, 2010). Avoidance of a long diagnostic quest is cited as the primary rationale for this endorsement.

Parents expressed belief that there was a rational process in place for considering the addition of new disorders to the newborn screening panel. However, this belief was not supported by the medical participants in this study, who voiced concern that advocacy groups and other lobbying forces appear to have more influence than scientific evidence.

Patient advocacy groups are not new to the political process involved in newborn screening. In a historical review, Paul (2008) described the influence of these groups from the inception of newborn screening, with advocacy groups cited as instrumental in the adoption of PKU screening. Indeed, patient advocacy groups increased the awareness of disparities in state screening panels leading to the formation of a federal advisory committee to recommend a uniform panel of tests. When the ACMG solicited input for their initial survey to determine which diseases belonged on this panel, private individuals and advocacy groups represented 60% of the responses (Paul, 2008). This finding lends support to the concerns of the medical participants. These participants assert that the legislation mandating KD screening was premature, that scientific evidence was insufficient, and advocacy group support superseded this evidence. Indeed, other experts have recommended against adding KD to the panel of newborn screening tests including the Secretary's Advisory Committee for Heritable Diseases in Infants and Children (Knapp, Kemper, & Perrin, 2009) based on review of existing evidence.

The theme *Unintended Consequences* included the unanticipated effects of the legislation adding KD to the newborn screening panel. Both positive and negative effects were found during qualitative analysis of the interview transcripts. One unintended consequence of KD screening for parents was an increased awareness of the disease. While increased awareness of a disease is not the intent of legislation, patient advocacy groups understand that by screening the population, awareness will increase as a result (Paul, 2008).

Medical participants discussed a heightened emotional response from parents when they received the notification of a positive KD screen. This response was regarded

as more intense than the usual response to positive newborn screen results. One parent discussed using pills, alcohol and cutting herself to deal with the pain of believing her infant was going to die, while another recalled that she was so ill physically that her milk dried up and she was unable to breast feed. These accounts reflect the medical participants' concerns. While there is evidence in the literature that parents are frightened about the possibility of their child having a disease (Farrell and Kuruvilla, 2008; Waisbren, et al., 2003), a thorough explanation of the disorder and treatment expectations can help reassure them. Perhaps the heightened response to KD screening results is explained by receiving incomplete or incorrect information about Krabbe disease or perhaps the uncertainty surrounding the confirmatory results contributed to parental recollection of the initial notification.

Another unintended consequence of KD screening was the latent fear that disease symptoms would appear. Waisbren, et al (2003) and Gurian, et al. (2006) found that parents continue to believe their child is affected even when the newborn screen has been confirmed as a false positive. However, after a positive KD screen, the confirmatory test results do not always provide the same certainty as other diseases on the newborn screening panel. Parents may be told their infant is at high or moderate risk to develop KD, or that their infant is a carrier of a disease causing gene. At the same time, physicians provide reassurance that their baby is neurologically normal, but to watch closely for anything strange. This diagnostic uncertainty creates what Timmermans and Buchchbinder (2010) refer to as "patients in waiting." They found that parents were likely to focus on the potential of disease rather than the reassuring message that their child had no symptoms and was doing well. In this study, parent participants recounted

watching closely for symptoms for the first year, admitting that even yawning, or blinking too often caused them concern. All of the parents interviewed commented about latent fear. Some parents were concerned that the confirmatory testing was not reliable; others were confused about the meaning of the risk categories; and all professed worry that their child could still develop KD at some point during the first year of life.

Medical participants provided the majority of the content found in the theme of *Knowledge and Science*. They discussed what was not known about KD, how screening has changed the knowledge about the disease, and compared KD to other disorders on the newborn screening panel. Since KD has been added to the New York newborn screening panel, there have been discoveries challenging what is known about the disease. These discoveries have not made diagnosing KD easier, but rather have increased the ambiguity surrounding low GALC activity and presence of disease. This ambiguity led to the conclusion published in a recent evidence review that “any screening for Krabbe disease be conducted in the framework of a research project,” (Kemper et al., 2010) p.543. Since infants are being identified with very low enzyme activity and mutations suggesting later onset disease (or novel mutations of unknown significance), providers are placed in a situation where counseling families about onset and severity of symptoms, as well as prognosis and treatment becomes difficult, because little is known about these forms of KD.

Medical participants asserted that the inability of the testing process to predict those affected or unaffected by disease should disqualify KD as part of the newborn screen. This lack of a predictive test has been documented by the researchers who conducted the UCBT treatment trial, who cite the need for predictive testing as “critical”

for those clinicians providing counseling to parents (Escolar, et al., 2009). This inability to provide counseling regarding symptom onset and prognosis left parents with more confusion and distrust described in the theme *Communication*. They knew their child has been diagnosed with something genetic, perhaps a disease that may progress to death, but are provided with no information, even from the specialists about what to expect.

Krabbe disease is not the only newborn screening test that has been controversial. Forty years ago, universal screening for PKU was controversial as well. Disagreement in treatment methods and unknown variation in the presentation and natural history of PKU led to infants being “over treated” with a protein - restricted diet (Brosco, Sanders, Seider, & Dunn, 2008). The treatment regimen for most metabolic diseases on newborn screening panels is dietary restriction of protein or addition of a vitamin supplement to the diet. If the infant is later discovered to not have the disease, liberalizing the diet easily reverses the treatment, and the effects of the restriction are quickly resolved. A systematic review of the literature and interviews of pediatricians involved in the controversy surrounding PKU treatment demonstrated that benefit of treatment far outweighed the burden of risk or cost in the rare overtreated patient (Brosco et al., 2008). With KD, however, the treatment is irreversible, carries a high risk of mortality and morbidity, and is less effective than initially reported.

Within the theme of *Communication*, parents described their experiences surrounding initial notification of their infant’s positive KD screen. According to New York State Public Health Law, hospitals or birth attendants are required to inform parents of the screening test (Test for phenylketonuria and other diseases and conditions. Public health law §2500-a, 2006). Despite this mandated requirement, more than half of the

parent participants were unaware their infant was screened in the nursery. Several studies point to the fact that parents are often unaware that newborn screening has occurred (Davis, et al., 2006; Grosse, et al., 2010; Bailey and Murray, 2008). For parents in this study, this lack of communication about newborn screening made the initial notification of a positive KD screen difficult for the parents.

Furthermore, the lack of information about KD from both the pediatrician and the metabolic specialists caused anxiety and lack of trust in the confirmatory results. Every parent participant commented about how frightening or confusing the initial notification of the positive KD screen was, and suggested that communication of reliable information could have made the experience better. Some parents were given information that was incorrect, others were not given information because the provider admitted not knowing about KD, and others were encouraged to look KD up on the newborn screening website. Participants described having more anxiety because they were unable to get information from the medical person they trusted, their primary care provider. As newborn screening panels are expanded to include more rare diseases, it may be difficult for these providers to keep abreast of the changes and take the time to learn about diseases they may never encounter. Time constraints in a pediatric practice make explanation of the complex genetic information now available from newborn screening difficult (Farrell & Kuruvilla, 2008; Davis, et al, 2006).

Medical stakeholders acknowledged that initial notification of a positive screening result could be difficult for parents to hear, and also that this communication was not always handled well. These participants agreed that there was insufficient knowledge about KD for them to provide comprehensive counseling to parents, and

argued this was a reason for KD to be removed from the newborn screening panel.

In the theme of *Moral Issues*, medical participants voiced concern about treatment for KD, a cord blood transplant performed prior to appearance of symptoms. While the UCBT study conducted at Duke showed initial promising results, questions about the long term effects of this treatment are emerging. There has been growing concern about progressive motor deterioration, lack of growth, and developmental delay (Duffner et al., 2009) and medical participants discussed their ambivalence about recommending this treatment to parents. Furthermore, UCBT has only been recommended as treatment for the early onset form of KD. For those infants identified with low enzyme activity and mutations who have not displayed symptoms, the treatment options remain experimental.

The concept of KD screening as research was also discussed by the medical participants. Many were concerned that KD screening constitutes research, as little is known about the natural history of the disease. The addition of KD to New York State's newborn screening panel in 2006 has been described as, "A grand experiment that changes lives" (Friedman, 2008). This creates an ethical dilemma for many of the medical stakeholders, as research without informed consent is a violation of the principle of autonomy. Since newborn screening in New York State is mandated, parental consent is not required for a test that ultimately may provide genetic information about carrier status or a disease that may not present symptomatically until adulthood. This type of predictive genetic testing is discouraged by many professional organizations, particularly when a disease has no treatment or cure (Borry, Stultiens, Nys, Cassiman, & Dierickx, 2006).

These concerns are reflected in the literature. Tarini, Burke, Scott, and Wilfond

(2008) described dangers of implementing newborn screening tests without adequate evaluation of efficacy and safety. Pilot studies in the context of quality improvement are undertaken to determine the efficacy and utility of a new test; however, population-based research that includes information about the nature of the disease, risks, benefits, and allowing voluntary participation is seldom conducted (Tarini, et al., 2008). As in the case of KD, the usual approach to adding a new test to a state newborn screening panel is to issue a legislative mandate to preserve public health (2008). Some medical participants discussed the fact that because KD is mandated, the need for informed consent no longer applies. Indeed, New York State does not require informed consent for newborn screening. Grosse, et al. (2010) endorsed a system of consent for those conditions with poorly understood natural histories or treatment of uncertain efficacy. These criteria certainly apply to KD. Obtaining informed consent for just one disease on the panel, however, has been found to be impractical, requiring more than an hour of additional staff time to obtain informed consent from parents (Haswega, Ferus, Ojeda, & Au, 2010). In California, during a pilot study of expanded screening using tandem mass spectrometry in California Researchers found that only 52% of families were offered the opportunity to participate in the expanded newborn screening; and, the lack of resources (i.e., staff time) to obtain consent was given as the reason for low participation. During the 18 months that the pilot study was conducted, it was calculated that 61 infants with a disorder detectable by tandem mass spectrometry were likely missed because informed consent was not obtained from parents (Feuchtbaum, L., Cunningham, G., Sciortino, S., 2007). Therefore, without a large increase in resources to obtain consent, which is not feasible in this political climate and with healthcare costs so high, obtaining consent does

not seem practical.

To assess the stakeholder perceptions of whether KD screening is meeting the goals of New York State newborn screening the goal must be broken into three parts. Medical participant interviews provided evidence to suggest that the addition of KD to the newborn screening panel fulfills the first part of the goal, “early identification of children at increased risk for selected metabolic or genetic diseases...”(New York State Department of Health, 2006b, p. 1-1). All medical participants agreed that infants at risk for KD are being identified.

However, questions were raised about KD screening meeting the second part of the New York State goal, “so that medical treatment can be promptly initiated to avert metabolic crises,” (2003, p. 1-1). While identification of the infants diagnosed with early infantile KD provided the option for prompt treatment, medical participants question whether crises had been averted, due to the medical procedures involved for UCBT. In addition, for the infants identified with low GALC enzyme activity and mutations suggesting a later onset of KD, there is no accepted treatment.

The third part of the goal, “and prevent irreversible neurological and developmental sequelae,” (2003, p. 1-1) was also contested by the medical participants. Cord blood transplant, even when initiated promptly, does not appear to prevent irreversible neurological and developmental sequelae (Duffner, 2009). Medical stakeholders were vocal in their concerns surrounding treatment. All the medical participants and program directors acknowledged that UCBT was not ideal. Although the treatment could delay onset of symptoms, those who received transplants would ultimately have disease progression. Medical participants compared the treatment for KD

to that of other disorders on the newborn screening panel to illustrate their concerns. Unlike the treatment for those disorders, UCBT is irreversible, has high morbidity and carries the risk of death. Medical participants expressed their reluctance recommending this treatment option to parents.

Aim 2.

Using quantitative methods, sensitivity, specificity and predictive values were calculated. Sensitivity is defined as the probability of a positive test given the presence of the target disease. Specificity is defined as the proportion of patients who do not have the target disease and who screened negative (Strauss, Richardson, Glasziou, & Haynes, 2005). The positive predictive value represents the precision of the test, in other words, the likelihood that a patient with a positive screen actually has KD. The negative predictive value represents the accuracy of the test, or whether the initial screening test correctly identifies those infants who do not have KD (Greenberg, Daniels, Flanders, Eley, & Boring III, 2006). Prevalence was also calculated and describes the number of people with a disease in a given population within a specified time frame. In newborn screening, it would be ideal to have a test with a sensitivity, specificity, and positive predictive value of 100% and a false positive rate of 0 (Sahai & Marsden, 2009). For the disorders on newborn screening panels, the cut-off points for reporting are set high in an attempt to eliminate false negative results, with the understanding there will be many false positive screens. To compensate for the expected number of false positives, the confirmatory test for the disorder should have a high positive predictive value to assure prompt treatment initiation, and avert morbidity or mortality. Since the positive predictive value is affected by the prevalence of a disorder, and all the disorders on

newborn screening panels are rare, the expected positive predictive value may be in the single digits (Reinaldo, Zafari, Tortorelli, & Matern, 2006).

The KD screening program has been effective at identifying infants with low enzyme activity with relatively few false positive results. After screening 1,062,000 infants in four years, the state reported 176 false positive results, and 9 infants with KD (enzyme activity ≤ 0.15 $\mu\text{mol/hr/mg}$ protein). Five of those 9 infants have no symptoms of KD, but are expected to develop a later onset form based on GALC mutations and minimal enzyme activity. Using these values, specificity was calculated at 100%, sensitivity was 99%, positive predictive value was 5%, and negative predictive value was 100%. Prevalence of KD was 1/100,000 births, which is consistent with values reported in the literature (Wenger, 2001). However, the state annual reports do not include those infants who have enzyme activity between 0.16 and 0.3 $\mu\text{mol/hr/mg}$ protein. These infants also have either GALC mutations that may develop into late onset KD, or mutations of unknown significance. If these infants were included in the state annual reports there would be 28 children with disease and 157 false positive results. Using these values to calculate the test characteristics, the specificity, sensitivity, and negative predictive value did not change, but the positive predictive value rose to 15%. The prevalence of KD increased to 3/100,000. Implicit in these calculations is the assumption that the infants identified at high or moderate risk will eventually develop KD. Kemper, et al. (2010) calculated the positive predictive value using only those infants identified with the early infantile form of KD. However, the legislation mandating KD screening does not specify screening for only one form of the disease; therefore all infants identified in the screening process should be included in the test calculations to

authentically represent the program.

The discrepancy in the annual reports is concerning, because all infants in the moderate and high risk categories were referred to neurology to undergo invasive neurodiagnostic testing and multiple follow up visits. This sends an ambiguous message to several stakeholders. Metabolic specialists inform parents that their child may be at risk to develop KD in the future and must be watched closely lest symptoms advance and treatment becomes unavailable, but the State doesn't classify the level of enzyme activity as KD. Parents are given a contradictory message that their infant is healthy and neurologically normal, but has the potential to develop a progressive neurologic disease. They are instructed to be vigilant in watching for symptoms, as well as attending regular neurology visits and invasive neurodiagnostic testing. Timmermans and Buchbeinder (2010) have described such children with biochemical features of disease but no symptoms, as "patients-in-waiting." If the intent of newborn screening is to identify infants early for treatment, then the confirmatory testing must be able to distinguish those affected with disease from those who are not affected. If this cannot be done, then there is insufficient knowledge about the disease, and further research must be conducted to support addition of a disorder to a newborn screening panel.

The discrepancy in projected referrals and resulting cost of the KD program was apparent in all data sources (see Aim 3 for further discussion of cost). In the text of the emergency rule legislation authorizing the addition of KD to the newborn screening panel, it was estimated that 25 newborns would be referred annually for confirmatory testing of the severe infantile onset form of the disease, and three would be confirmed with disease (Expansion of the New York State newborn screening panel, 2006). In

practice, however, these numbers are quite different. A total of 185 infants were referred from August 2006 through July 2010. Of those referred, four infants have been diagnosed with early onset KD, another five infants have been categorized as “high risk to develop KD,” and the remaining 19 are categorized at “moderate risk to develop KD.” The expert consensus recommendation is that infants in both risk groups follow a schedule of neurology and neurodiagnostic follow up (Appendix 2). When the emergency rule legislation was enacted, the later onset forms of KD were not considered, since the literature reported these forms were very rare.

Aim 3.

Data sources were selected to represent urban and rural regions of the state, as well as a variety of reimbursement sources. The cost categories were chosen to represent the procedures and consultations outlined in the consensus protocol developed by the Krabbe Consortium (Appendix 2). The annual cost of adding KD to the screening panel was estimated to be \$750,652. This cost fell below the increased State appropriation of \$2,000,000 (\$11,000,000 in 2006 from \$9,000,000 in 2005) (Governor Pataki introduces 2006-07 executive budget, 2006).

From the State perspective, the cost of this program may not be excessive, given the cost of other disorders on the panel, like severe combined immunodeficiency and other inherited T-cell deficiencies (SCID). In March 2011, SCID was added to the New York State newborn screening panel. SCID was recommended by the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children and became the 30th disorder on the uniform screening panel (Bonhomme, 2010). This disorder is similar to KD in that it is rare (New York State estimated that 6 infants would be referred for

transplant annually (Expansion of the New York State newborn screening panel, 2011), the screening laboratory test is similar, and early treatment is most efficacious. A cost utility analysis conducted by McGhee, Stiehm, and McCabe (2005), determined the cost to detect and treat one case of SCID to be \$485,000. SCID is different than KD in that the disorder can be cured with a bone marrow transplant (McGhee, Stiehm, & McCabe, 2005).

The average direct medical cost to a family whose infant has a positive confirmatory test is estimated at \$2,669, which could be excessive, depending on whether or not the family has health insurance to cover the costs associated with the positive confirmatory testing. This cost could represent hardship for families without insurance or with high copays and deductibles. The cost estimate in the emergency rule text for KD included confirmatory enzyme testing, spinal fluid analysis (without compensation for the lumbar puncture procedure), a single office visit to the specialty center, a genetic counseling appointment, and a post-transplant MRI. The total estimate in the emergency rule legislation was \$550 for an infant with a positive KD screen, and an additional \$2700 for an infant who received a transplant (Expansion of the New York State newborn screening panel, 2006). No further follow up was anticipated after a transplant was performed.

To fully appreciate the cost of newborn screening, Hubbard (2007) asserts that the following must be considered: instrumentation; labor and time; initial, repeat, and confirmatory testing; screening test sensitivity and specificity; and short and long-term follow up. The emergency rule legislation costs were based on the assumption that the confirmatory test for KD would identify infants for immediate treatment, but did not

consider costs subsequent to UCBT, nor the treatment costs. There was also no consideration for the total cost of the neurodiagnostic work up for every infant with a positive confirmatory test. The asymptomatic infants are referred for ongoing long-term follow up including neurodiagnostic tests to monitor for development of KD symptoms.

Cost analyses evaluating newborn screening tests are used as a decision aid versus a rule, and their use is not supported in the US when making policy funding decisions (Grosse, Teutsch, and Haddix, 2007). These authors describe the difficulty in assessing economic evaluations for rare disorders included in newborn screening panels, in part because often little is known about long-term adverse outcomes of these disorders (2007). This is certainly true for the later onset forms of KD.

Brosco, et al. (2008), discussed a commentary by Joseph Cooper, a political scientist attending a conference about PKU screening in 1965, which provides a context for considering the costs of newborn screening. Cooper wondered whether the experts had lost sight of the larger problems facing the United States and children in particular, noting high rates of poverty, limited access to health care, and an unpopular war. He then wondered why we have mandatory state laws to identify rare disorders that we do not completely understand (Brosco et al., 2008). These comments hold true today, and serve as a reminder that we must consider cost in the context of other health issues affecting children today.

Carroll and Downs (2006) calculated the cost of tandem mass spectrometry newborn screening for 29 disorders compared screening to be \$4839 per QALY saved over not screening, and concluded that newborn screening programs as a whole are cost-saving. However, their analysis only included those disorders in the uniform panel

recommended by the Secretary's Advisory Committee on Heritable Conditions in Newborns and Children, and KD is not included in that panel.

Study Implications

Strengths and Weaknesses

In qualitative studies, trustworthiness is the measure of scientific rigor, and is generally described in terms of credibility, transferability, dependability, and confirmability (Miles & Huberman, 1994). Credibility is the concept of congruency of research findings and the collected data. Credibility is often compared to the quantitative concept of internal validity (Shenton, 2004). One strategy used to achieve credibility was the use of the CDC Framework for Program Evaluation in Public Health (1999). This framework provided a well-established guidelines and standards of conduct for the investigator. To further insure credibility, assurance of study participant anonymity was employed to allow for frank and honest discourse. Transferability mirrors the quantitative concept of external validity (Shenton, 2004). This was addressed by providing a complete description of the documents analyzed, participants, data collection sites, the interview process, and time frame of the data collection. Dependability concerns the quality of the data collection, analysis and generation of conclusions (Shenton, 2004). To achieve this, the research design and methods were reviewed by committee at the investigator's dissertation proposal and by the Columbia University Institutional Review Board prior to actual data collection. Confirmability represents how well the study findings are supported by the data. This was achieved by a process described by Miles and Huberman (1994) as "check-coding." The dissertation sponsor reviewed these codes in an ongoing manner and refinements were made as agreement was reached between the investigator

and the committee. Member checks for medical participants were accomplished by presenting findings at the Krabbe Consortium meeting, allowing medical participants the opportunity to comment on emerging themes. The investigator contacted a subset of parent participants by telephone to review selected portions of the interview transcripts.

To maximize diversity of the data, the technique of data triangulation was used. Data were collected from printed and electronic sources as well as personal interviews. Content analysis of supporting documents provided the description of the KD screening program as well as providing the background for the interview guides (Appendices 5 and 6). Face-to-face interviews and telephone interviews were conducted to collect data from study participants and analyzed using the qualitative technique of content analysis. Quantitative methodology was used to analyze KD screening results and calculate test characteristics and cost of the screening program. The triangulation of results provided a comprehensive evaluation of the program.

The use of a single interviewer can be viewed as both a strength and a weakness. A single interviewer decreased variability of the interview process. However, the use of a single interviewer may introduce bias. The interviewer/investigator is employed as a pediatric nurse practitioner at one of the metabolic specialty centers. She is involved with reporting KD screening results to parents, interaction with parents during evaluation at the specialized care center, and assuring follow-up if confirmatory enzyme testing is positive. Every effort was made to assure objectivity and the nature of the investigator's involvement in the newborn screening process was fully disclosed to all participants. A thorough description of the data collection process was provided at the dissertation proposal, and the investigator wrote field notes during and after each interview to reflect

and refine the data collection process. The investigator attended weekly meetings with her dissertation advisor to address concerns and to uncover potential confirmation bias of the findings.

Sample bias may be a weakness of this study; subjects were not randomly selected, but were selected for their involvement with KD screening. Additionally, none of the parent participants in this study had a child in the high-risk category, one child was in the moderate risk category, and the remaining children were at no risk to develop KD, but could be carriers of KD. Furthermore, those parents and clinicians agreeing to be interviewed may have had a particularly bad experience or opinion. Therefore, the perceptions of these participants may not reflect the perceptions of all people involved with KD screening. To address potential sample bias, purposive sampling of participants was used as a strategy to assure credibility. This strategy allowed for a participant pool that had adequately experienced the program under study, and recruitment was conducted in both rural and urban areas of New York State to address potential geographic bias. To further address the concern that parent participants included only those with favorable or unfavorable impressions of the KD screening program, the technique of theoretical saturation was used. Theoretical saturation refers to the point at which no new information is being found. Furthermore, the participant sample in this study was exclusively Caucasian. Due to financial limitations, the investigator was unable to provide necessary translation services to recruit families that did not speak English. Therefore, only families who spoke English were recruited for participation. This requirement eliminated 31 participants from the prospective study sample. Another limitation was the lack of primary pediatricians in the study sample. Due to limited

resources, primary pediatricians, although involved in the parental notification of KD positive results were not invited to participate.

There were additional limitations in the cost analysis. The assumptions made for the cost analysis were based on best available data, which may be incomplete. Long-term costs and outcomes, including treatment of KD were not included in this analysis, nor was the impact of nonmedical costs. For those infants with low GALC activity, the costs of medical follow up after confirmatory enzyme testing were also not included in this analysis. Although the resulting simple cost analysis is limited, it is the first analysis of any cost data associated with KD screening.

Practice and Policy Recommendations

There are a number of important practice and policy recommendations resulting from this research. First, public awareness of newborn screening should be improved. Despite the legislative mandate that information about newborn screening must be provided to parents, there appears to be a lack of awareness about the process. This information could be provided to parents during routine obstetrician visits, while parents are learning about what to expect when their baby is born. During the hospital stay, both nursery personnel and pediatricians could reinforce this information to decrease the potential shock of a positive screen.

Second, communication of positive KD screening results to parents should be improved. Because pediatricians may lack both the knowledge and time to properly assure parental understanding of a positive KD screen, these results should be communicated by the metabolic specialists more familiar with both KD and the complex genetic information accompanying a positive KD screen. The pediatrician could initiate

contact with parents, informing them that a metabolic specialist will be contacting them with information about their infant's newborn screen. This could allow the pediatrician to facilitate communication while removing the burden of explaining KD to parents and still maintaining the role of the medical home. By allowing the metabolic specialist to deliver the information about KD, the potential for incorrect information is decreased.

Third, since KD testing has the potential to identify infants with low-enzyme activity and mutations suggestive of later onset forms of this disease, the moral principle of autonomy must be addressed. Instituting an informed consent process for KD testing could inform parents of the potential implications of a positive result. Informed consent would also address the concerns expressed by the medical participants in this study that New York State is conducting research without parental consent. When newborn screening and consent have been studied, when consent is offered, very few parents decline screening; however, the process of obtaining consent is resource intense (Feuchtbaum, Cunningham, & Sciortino, 2007). For this reason, instituting informed consent for routine newborn screening is not recommended.

Fourth, an improved reporting strategy should be considered. Minimally, a category of "indeterminate" should be added to the State Annual Report to represent the infants who have developed KD and those who are asymptomatic, but at risk to develop disease. This reporting system would more accurately reflect the results of the KD screening program.

While the addition of KD to New York State's newborn screening panel has identified four infants with the early infantile form of the disease, there have been 24 infants deemed at high or moderate risk to develop KD later in life. Since neither the

confirmatory enzyme test nor the neurodiagnostic tests can accurately provide a prognosis or accurate information about onset or severity of symptoms, the ability to determine those affected from those unaffected is limited. In addition, the neurodiagnostic testing itself carries a level of risk, as the MRI is performed under anesthesia. Furthermore, the only available treatment for KD, a UCBT performed prior to onset of symptoms, is irreversible and carries a high rate of mortality and morbidity. This treatment is now thought to only delay onset of symptoms and it is not known if those infants transplanted will eventually die from KD. Therefore, the goal of preventing irreversible neurological and developmental sequelae is not being met. Since the goals of New York State newborn screening are not satisfied, it is recommended that KD be removed from the screening panel.

Recommendations for Further Study

There are a number of recommendations for further research resulting from this study. First, ongoing concerns regarding UCBT for KD support the need for long term, longitudinal follow-up of children who have been transplanted for KD. These studies should include quality of life measures, as no studies have been published addressing this issue. Furthermore, the infants transplanted in the Duke study (Escobar et al., 2005) all had siblings with KD, and parents watched these siblings die. This population is different than infants identified through newborn screening, whose families have no experience with KD, and this difference may influence the decision to pursue UCBT. As other states begin to screen for KD, a national database could be used to track the outcomes of these children.

Second, to fully study the cost of KD, and evaluate the contribution of newborn

screening for this disorder, a cost effectiveness analysis should be conducted, comparing screening for KD to not screening. This analysis should include direct and indirect costs of screening, medical follow up, and current treatment costs for KD, as well as the costs for those who have been identified at high or moderate risk, but are asymptomatic. More economic analyses are needed to address the cost of KD testing from the societal perspective. While economic evaluations do not affect whether or not a policy is adopted in the US, these evaluations can provide scientific, rather than colloquial evidence about the costs associated with KD. These cost studies would provide information that is currently unavailable for KD and inform those who must make decisions regarding allocation of resources.

To determine the significance of novel mutations and the combinations of mutations known to cause later onset disease, studies are needed to follow these infants to age of onset. A well-designed longitudinal study should include age of onset of symptoms, events surrounding onset of symptoms, and any medical surveillance. These studies are vital to gain understanding of the genetic data being discovered as a result of KD newborn screening. A national database would be one way to organize these data. This type of study may be difficult for several reasons, including: parents not wishing to participate in this type of research, families lost to follow up, and insufficient staffing resources to collect and enter data.

Additionally, publication of the mutations discovered as a result of the KD newborn screening program in New York should be encouraged. This information could provide useful information to those states that have passed legislation to begin KD screening programs.

A major limitation of this study was the exclusion of non-English speaking families. Little is known regarding the effect of newborn screening results and genetic information for families from different cultures, and results from studies could help providers understand and address concerns that may be currently unrecognized.

There is a need for well-designed studies that address parental lack of knowledge regarding newborn screening. Questions to consider involve; who should inform parents, timing of this information, and what information would be most useful. Results from these studies could provide information helpful to clinicians and state labs to design effective education for parents. Primary care providers may be unaware of the process involved with newborn screening and confirmatory testing, and may lack knowledge about some disorders included in the panel. The need exists for studies to determine educational needs of primary care providers and how best to meet those needs so factual information can be provided to parents. Interviews with pediatricians could also be conducted to assess their perceptions of KD screening and to determine their knowledge of the disease.

It is unknown what effect a positive KD screen has on parents and families. There is evidence to suggest that false positive newborn screen results have psychological effects on parents (Waisbren, et al.), but little is known about the effects of “at risk” results. For those infants at risk to develop KD, neurologic follow up and neurodiagnostic testing continues for years. Research should focus on the impact of KD screening for families with infants in the high and moderate risk groups.

Dissemination Plan

The final step of the CDC Framework is to ensure and share the lessons learned in

the evaluation. During the course of this study, preliminary results have been presented in an ongoing process. Peer scrutiny of the research was elicited by presentation of preliminary study findings at the Lysosomal Storage Diseases Conference in February 2010 and as a poster presentation at the annual Academy Health meeting in June 2010. Preliminary findings were also shared at the Krabbe Consortium meeting in December 2010. This presentation was used to elicit member checks of the qualitative results from the medical participants, allowing the opportunity to comment on the emerging themes.

Results of this evaluation will be submitted for publication to reach the broadest audience possible. To reach health policy decision makers, a manuscript will be submitted to a high impact journal, such as *Health Affairs* or the *American Journal of Public Health*. To reach an audience of genetic practitioners, a manuscript submission to the *Journal of Inherited Metabolic Disease* is planned. Participants will be notified of any publications resulting from this study.

Conclusions

Since 2006, there have been more than 1,000,000 infants screened for KD in New York State. While the screening has identified four infants with the early infantile form of the disease, there have been 24 others identified with low enzyme activity and mutations that may cause later onset forms of the disease, which are poorly understood. This unexpected finding suggests that newborns may be diagnosed with a disease that may not present symptomatically until adulthood. Unfortunately, the current confirmatory enzyme test and neurodiagnostic tests cannot predict onset of disease or severity of symptoms. In addition, the only available treatment, a cord blood transplant, is irreversible, has a high risk of morbidity and mortality, and long term outcomes have not been studied. While the

cost of the program from the perspective of the state is not excessive, cost-effectiveness studies are needed to determine the cost of KD screening from the societal perspective, and should include treatment and follow up costs.

In conclusion, screening for KD does not meet the stated goals of the New York State newborn screening program. Parents are in need of more education about newborn screening, and pediatricians should work closely with metabolic specialists to deliver positive results to parents to minimize the potential for incorrect information. In addition, the State should institute a reporting system that adequately reflects all the infants being identified as a result of KD screening. More research is needed to understand the mutations being identified as a result of KD screening, to follow the long term outcomes and quality of life for those children who have received cord blood transplants, and to appreciate the impact of a positive KD screen on parents and families.

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Appendix 1: Survey Scoring criteria from the ACMG Task Force on Newborn Screening
(Brameld, K. 2006)

The Condition/Disorder	Categories	Score
Incidence of Condition	>1:5,000	100
	>1:25,00	75
	>1:50,000	50
	>1:75,000	25
	<1:100,000	0
Signs & symptoms clinically identifiable in the first 48 hours	Never	100
	<25% of the cases	75
	<50% of the cases	50
	<75% of the cases	25
	Always	0
Burden of disease (natural history if untreated)	Profound	100
	Severe	75
	Moderate	50
	Mild	25
	Minimal	0
The Test for the Condition/Disorder		
Does a sensitive & specific screening algorithm already exist?	Yes	200
	No	0
Test characteristics Yes=apply score No=zero	Detectable in neonatal blood spots or by a simple nursery physical method	100
	High throughput >200/day/FTE	50
	Overall analytical cost <\$1 per test/condition	50
	Multiple analyses relevant to one condition in same spot	50
	Other conditions detected by some analyses	50

	Multiple conditions detected by the same analytes	50
	Multiple conditions detected by the same test (multiplex pattern)	200
The Condition/Disorder Treatment		
Availability of treatment	Treatment exists & is widely available in most communities	50
	Treatment exists, but availability is limited	25
	No treatment is available or necessary	0
Cost of treatment	Expensive (>\$50,000/patient/year)	50
	Inexpensive (<\$50,000/pt/yr)	100
Potential efficacy of existing treatment	To prevent ALL negative consequences	200
	To prevent MOST negative consequences	100
	To prevent SOME negative consequences	50
	Treatment efficacy is not known	0
Benefits of early intervention (Individual outcome)	Clear evidence that early intervention resulting from newborn screening optimizes outcome	200
	Some evidence that early intervention resulting from newborn screening optimizes outcome	100
	No evidence that early intervention resulting from newborn screening optimizes outcome	0
Benefits of early intervention (Family & society)	Early intervention provides clear benefits to family & society (education, understanding prevalence, natural history and cost-effectiveness)	100
	Early intervention provides some benefits to family and society	50
	No benefits to family and society	0
The Screening Program		
Early diagnosis & treatment prevent mortality	Yes	100
	No	0
Availability of diagnostic confirmation	Wide	100
	Limited	50

	Poor	0
Acute management	Providers of acute management widely available	100
	Limited availability of qualified providers of acute management	50
	Acute management of available in city in a few centers	0
Simplicity of therapy	Management at primary care or family level	200
	Requires periodic involvement of a specialist	100
	Requires regular involvement of a specialist	0

Appendix 2: *Krabbe Consortium Evaluation Schedule and Point System for UCBT*

Evaluation Schedule (for infants with positive confirmatory enzyme results)

	<u>Neurological Evaluation</u>		<u>Neurodiagnostic*</u>
High Risk (0.0-0.15)	Year 1	Q Month	Baseline, then Q4 months X 3
	Year 2	Q 3 Months	PRN**
Moderate Risk (0.16-0.29)	Year 1	Q 3 Months	Baseline, then PRN**
	Year 2	Q 3 Months	PRN**

*MRI, Lumbar Puncture, Nerve Conduction Velocity, Brainstem Auditory Evoked Responses

** Only if abnormal neurologic exam or developmental/functional delays

Neurodiagnostic Studies

- MRI Brain
 - 4 or 5 mm slices with 1 mm interslice gap or no gap
 - Axial unenhanced T1 weighted images
 - Axial flair images
 - Sagittal proton-density and T2 weighted images
- Lumbar Puncture
 - Protein – abnormal if > 25 mg/dl above norm for age
 - Cells
- BAER
 - Abnormal if (1) prolongation interpeak latency I-V or (2) loss waves III-V
- Nerve Conduction Velocity (one sensory and one motor in one upper and one lower extremity)
 - Abnormal if:
 - Absent response
 - F waves unobtainable or with prolonged latency

- Prolonged distal latency
- Slow conduction velocity
- Conduction block > 50% reduction of CMAP amplitude proximal vs. distal (partial)
- Conduction block (complete) loss CMAP on proximal stimulation

Point System For UCBT Referral

Consider Transplantation for scores ≥ 4 Points

	<u>Points</u>
• Abnormal Neurologic Exam	2
• Positive MRI	2
• Positive LP (Increased Protein)	2
• Positive NCV	1
• Positive BAER	1
• DNA analysis: 30 Kb Homozygous Deletion	4

Appendix 3: *Parent Abstract and Invitation Letter*

Information About the Krabbe Disease Screening Program Evaluation Study:

The purpose of this study is to conduct a formal program evaluation of newborn screening for Krabbe disease in New York State using the CDC Framework for Program Evaluation in Public Health. The aims of this study will be: 1) Assess if Krabbe disease screening is meeting the stated goals of the New York State newborn screening program for each of the stakeholders using this program 2) Assess the Krabbe disease test characteristics with the most recent data available, and 3) Assess the cost to identify one true positive Krabbe disease screening result.

Members of various stakeholder groups will be invited to participate in one to two hour audio-taped interviews. Stakeholders include individuals with a child who screened positive for Krabbe disease, nurse practitioners, genetic counselors, medical directors, parent advocacy group representatives, and directors of operations involved in the Krabbe disease screening program. These stakeholders represent people involved in program operations, people served or affected by the program, or people in a position to make decisions about the program. Gathering information directly from stakeholders is thought to provide relevant data for analyzing the effectiveness of the Krabbe disease screening program as described by New York State.

The student investigator will conduct opened ended interviews using guides designed for each stakeholder group. The interviews will be transcribed and analyzed using the qualitative method of content analysis. It is expected that 28 interviews of about 1 hour per interview will be conducted, with members from each stakeholder group represented.

Bobbie Salveson is the student investigator for this study. She is a pediatric nurse practitioner pursuing a research doctorate at Columbia University School of Nursing, with an interest in health policy. She is involved in the newborn screening program as the coordinator for newborn screening at the Mount Sinai specialty metabolic center in New

York City. If you are interested in participating in this study, please send the stamped postcard and she will contact you to arrange an interview at a time and place convenient for you.

Dear Parent,

In August of 2006, New York State became the first and only state to implement testing for Krabbe disease, a rare neurological disorder. This program has screened over 800,000 infants since that time, and other states are considering adding this test to their newborn screening panel. The need exists for an objective evaluation of this program to provide information to people involved in health policy decision-making. Therefore, a research study is being conducted to provide this information.

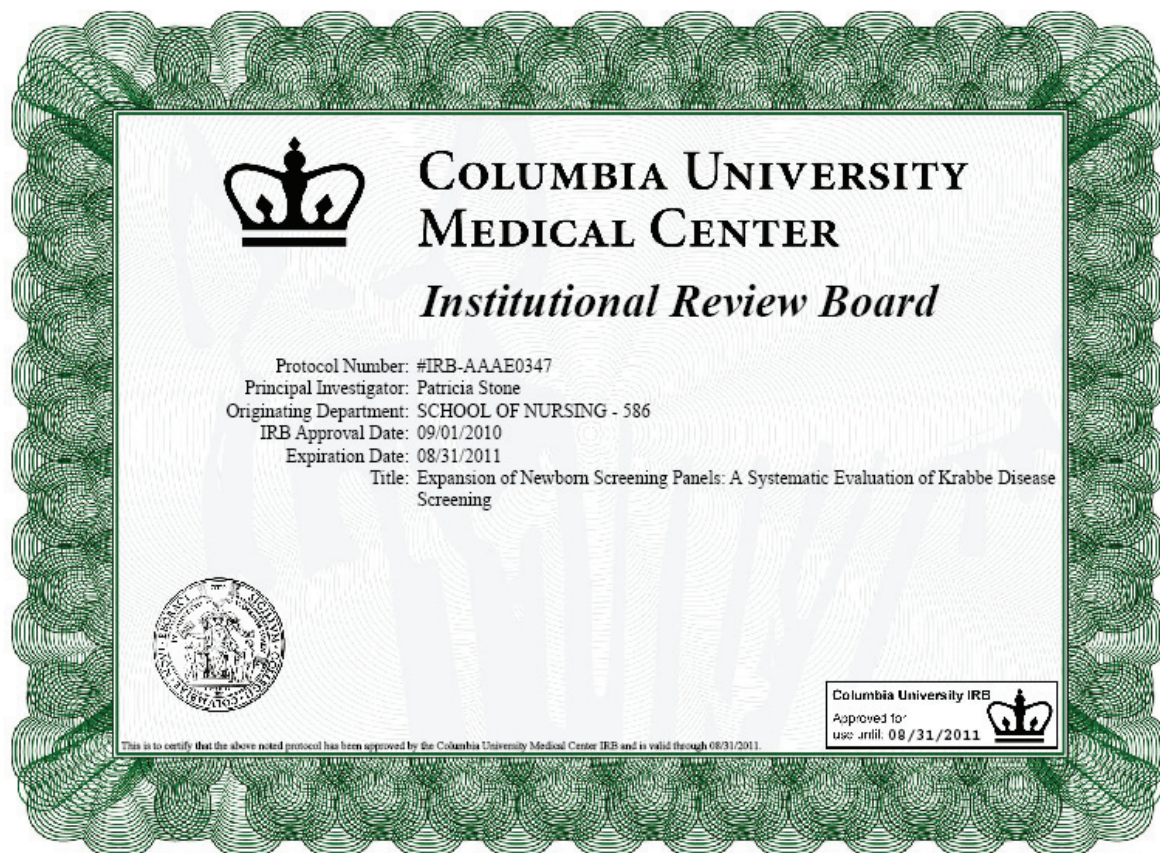
The purpose of this study is to conduct a formal program evaluation of newborn screening for Krabbe disease in New York State using the CDC Framework for Program Evaluation in Public Health. Stakeholders in the Krabbe disease-screening program will be contacted and interviewed using semi-structured interview guides. These interviews will be analyzed using qualitative research methods, reviewed, and the results of the study will be published in an academic journal. It is hoped that this research study will provide information for public health decision makers considering the addition of screening for Krabbe disease in newborns.

You have been invited to participate in this study because you are a stakeholder in the Krabbe disease-screening program, and your child was evaluated at the Metabolic Specialty Center. Stakeholders include individuals with a child who screened positive for Krabbe disease, nurse practitioners, genetic counselors, medical directors, parent advocacy group representatives, and directors of operations involved in the Krabbe disease-screening program.

If you are interested in participating, please return the stamped postcard enclosed, and the investigator will contact you to arrange an interview at a place and time convenient to you. I will have no way of knowing whether you responded, or participated in the study, and will not contact you again regarding your participation. The investigator of the study will contact you confidentially, and you are under no obligation to participate.

Thank you for considering participation.

Sincerely,

Appendix 4: *IRB Certification and Stamped Consent Form*

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAE0347

Principal Investigator: Patricia Stone (ps2024)

IRB Protocol Title: Expansion of Newborn Screening Panels: A Systematic Evaluation of Krabbe Disease Screening

Consent Number: CF-AAAG6716

Participation Duration: 1 hour

Anticipated Number of Subjects: 28-32

Contact

Contact	Title	Contact Type	Numbers
Roberta Salvesson	PNP	Co-Investigator	Telephone: 347-513-6068 Pager: 212-241-7055
Patricia Stone	PhD	Principal Investigator	Telephone: 212 305 1738

Research Purpose

The purpose of this study is to conduct a formal program evaluation of newborn screening for Krabbe disease in New York State.

Information on Research

WHY IS THIS STUDY BEING DONE?

In August of 2006, New York State became the first and only state to implement testing for Krabbe disease, a rare neurological disorder. The purpose of this study is to conduct a formal program evaluation of newborn screening for Krabbe disease in New York State using the CDC Framework for Program Evaluation in Public Health. We will interview stakeholders in the Krabbe disease screening program using semi-structured interview guides and will analyze the data. We hope that this research study will provide information for public health decision makers considering the addition of screening for Krabbe disease in newborns.

You have been invited to participate in this study because you have been involved in the Krabbe disease screening program and are someone who is involved in program operations, is served or affected by the program, or someone who is in a position to make decisions about the program. Stakeholders include individuals with a child who screened positive for Krabbe disease, nurse practitioners, genetic counselors, medical directors, parent advocacy group representatives, and directors of operations involved in the Krabbe disease screening program.

WHAT IS INVOLVED IN THIS STUDY?

Medical Center Institutional Review Board: 212-305-5993
 Consent Form #: CF-AAAG6716 Copied From: CF-AAAE7748
 Printed On: 04/19/2011 at 02:02 page 1 of 4



Procedures

A single interview will be conducted in person by the investigator or by telephone. This interview will be scheduled at your convenience and last 1 to 2 hours.

Permission for future contact

The researchers may want to contact you in the future if clarification is needed regarding something in the interview and/or to review the analysis of your interview.

Please initial below to show whether or not you give permission for future contact.

_____ (initial) Yes, I give permission to be contacted in the future for information relating to this study.

_____ (initial) No, I do not give permission to be contacted in the future for information relating to this study.

Audio recording

We will record the interview using audiotape so that it can be analyzed by our research team. Having your interview recorded is required to take part in this study.

The recording will include a code number assigned by the principal investigator to identify you. Your name will not be linked to this number on the recording, and the document linking your name and number will only be accessible by the investigator.

The recording will be stored in a locked file cabinet and linked with a code to your identity and will be retained indefinitely.

INTRODUCTION

The purpose of this form is to give you information to help you decide if you want to take part in a research study. This consent form includes information about: why the study is being done and the things that you will be asked to do if you are in the study.

The student investigator (the lead researcher for this project) will discuss the study with you. If at any time you have questions about the study, please ask the investigator or her advisor. Take all the time you need to decide whether you want to take part in this research study.

Risks

WHAT ARE THE RISKS OF THE STUDY?



Inconvenience

Although it is not a risk, taking part in this study involves the inconvenience of giving an hour or two of your time in order to participate in an interview about your experience with Krabbe disease screening.

Benefits

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You will not receive personal (direct) benefit from taking part in this research study. However, the information collected from this research may help others in the future.

Confidentiality

WHAT ABOUT CONFIDENTIALITY?

Confidentiality Protection

Any information collected during this study that can identify you by name will be kept confidential. We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely.

Your taped interview response will be assigned a code number to protect your confidentiality. Your name will not be kept in the same place as the code. It will be kept in a locked file cabinet and only the investigator and study staff will have access to the file.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff and other professionals who may be evaluating the study
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB')

Compensation

WILL I GET COMPENSATED?

You will not receive any payment or other compensation for taking part in this study.

Additional Costs

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study.

Voluntary Participation

DO I HAVE TO BE IN THE STUDY?

Participation in this study is voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may discontinue participation at any time without

penalty or loss of benefits to which you are otherwise entitled.

Additional Information _____

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions or concerns about the study, you may contact Bobbie Salveson at 347-513-6068 or Dr. Patricia Stone at 212-305-1738.

If you have any questions about your rights as a subject, you may contact:

Institutional Review Board

Columbia University Medical Center

722 West 168th Street, 4th Floor

New York, NY 10032

Telephone: (212) 305-5883

An Institutional Review Board is a committee organized to protect the rights and welfare of human subjects involved in research.

Statement of consent

I have read the consent form and talked about this research study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing to take part in this research study and that I can stop being in the study at any time. I am not waiving (giving up) any of my legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Signature

Principal Investigator

Print Name _____ Signature _____ Date & Time _____

Study Subject

Print Name _____ Signature _____ Date & Time _____

Person Obtaining Consent

Print Name _____ Signature _____ Date & Time _____

Appendix 5: *Initial Interview Guides*

Stakeholder Group: Those involved in program operations (Medical)

Consent Signed: _____

Date & Time of Interview: _____

Interview Location: _____

Demographic information: Years in practice _____

Position _____

Political Process

What was your role in implementing the Krabbe disease screening program?

Information Seeking

Tell me about your experience with the program since screening began.

Projected Referrals

Tell me about any newborns referred that screened positive?

How many?

What did the confirmatory testing show?

Parent Notification

Describe your contact with parents who have had children that screened positive

Use of Consortium Protocol - Consistency

Tell me about your Krabbe Disease protocol?

How is the protocol used in your setting?

Krabbe Consortium Feedback

Are there any improvements you would like to see with the program?

Describe any changes made to the program since implementation

Meeting goals of NYS newborn screening

How does the Krabbe disease screening program compare to screening for other disorders?

Stakeholder Group: Those served or affected by the program (Parent)

Consent Signed: _____

Date & Time of Interview: _____

Interview Location: _____

Demographic Information: Gender _____ Age _____ Number of
children _____ Metabolic Referral Center _____***Parent Notification***

How did you first hear that your child had a positive newborn screen?

Were you aware your child had been screened in the nursery?

Information Seeking

Describe your experience with the follow-up for Krabbe disease screening

Indirect Costs

Can you tell me about any difficulties or inconveniences you experienced associated with the follow-up?

Direct Costs

Tell me about any medical costs associated with the follow up:

Clarity of Information

What kind of results and recommendations did you receive from the providers caring for your child?

Impact of Screening

Since the screening, can you tell me about anything that has changed in your child's health?

And with your family?

Political Process

Can you suggest any ways this process might have happened differently?

Appendix 6: *Final Interview Guides*

Stakeholder Group: Those served or affected by the program (med)

Consent Signed: _____

Date & Time of Interview: _____

Interview Location: _____

Demographic Information: Years in Practice: _____

Position: _____

Political Process

Tell me about your role in implementing the Krabbe disease screening program

Information Seeking

What has been your experience with the program since screening began?

Projected Referrals

Tell me about any newborns referred to you for positive screens

And their confirmatory testing?

Lessons Learned

Do you have any concerns about these results?

Parent Notification

Describe your contact with parents of children who have screened positive.

From initial notification to discharge – ***added to clarify and assess process***

Use of Consortium Protocol - Consistency

Describe your center's use of the follow up protocol established by the Krabbe disease Consortium:

To the best of your knowledge – how are families adhering to the recommendations? discharge – ***added to clarify and assess process***

Parent Notification

Describe any issues parents have had with the screening process

Krabbe Consortium Feedback

Any changes you've seen based on feedback from the Consortium meetings?

Political Process

Are there any improvements you would like to see with this program?

Meeting goals of NYS newborn screening

How do you think Krabbe disease screening fits the newborn screening model established by New York State?

Meeting goals of NYS newborn screening

How does Krabbe disease screening compare to screening for other disorders?

Meeting goals of NYS newborn screening

Since implementation – can you think of anything that has been learned that could be applied to make the screening process as intended?

Lessons Learned

What kind of issues in this program have been frustrating for you as a physician?

Lessons Learned

Describe the successes of the Krabbe screening program

Political Process

If you were offering guidance to decision-makers in other states, what would you tell them about implementing a Krabbe screening program?

Stakeholder Group: Those served or affected by the program (parent)

Consent Signed: _____

Date & Time of Interview: _____

Interview Location: _____

Demographic Information: Gender _____ Age _____ Number of
children _____ Metabolic Referral Center _____***Parent Notification***

How did you first hear that your child had a positive screen?

Information Seeking

Describe your experience with the follow-up for Krabbe disease screening.

How could this have been made better for you?

Information Seeking

Tell me about any information resources available to you about screening.

Indirect Costs

Can you tell me about any difficulties or inconveniences you experienced associated with follow - up?

Clarity of Information

What kind of results and recommendations did you receive from the providers caring for your child?

Impact of Screening

Since the screening, can you tell me about anything that has changed in your child's health (or your family)?

Impact of Screening

Tell me about any concerns you may have - are these related to the Krabbe screening process?

Political Process

Do you have any suggestions for other parents going through this process?