TITLE: Newborn Screening for Krabbe Leukodystrophy: A Review of the Clinical and Cost Effectiveness and Guidelines

DATE: 17 February 2012

CONTEXT AND POLICY ISSUES

Krabbe disease belongs to a group of genetic disorders, referred to as leukodystrophies, that affect the growth of the protective coating around the peripheral and central nervous system.\(^1\) The disease is caused by the deficiency of an enzyme called galactocerebrosidase (GALC).\(^1\) The incidence of the disease is estimated to be 1 per 100,000 births in Europe and the united states.\(^2\)

There are two forms of Krabbe disease:

(a) Early-onset disease (85%-90% of cases) appears in the first few months of life. The infantile disease present with progressive neurologic deterioration.
(b) Late-onset disease (10%-15%) may begin in late childhood or up to fifth decade of life. This form of the disease has slower progression rate.\(^3\)

Krabbe disease is usually diagnosed after the onset of symptoms. The diagnosis can be established or confirmed by measurement of the GALC enzyme activity in white blood cells.\(^3\) Molecular testing for GALC gene defects is also available and may be used for carrier detection in at-risk relatives of diagnosed cases.\(^3\)

The prognosis of the disease is poor, especially in infants with early-onset disease. The majority of these children die before age two.\(^3\) Early diagnosis of Krabbe disease can be important, especially for the infants with this form of disease, because some studies have shown the therapeutic benefit of stem cell transplantation before the development of symptoms.\(^4,5\) Recent advances in newborn screening technologies has led to the availability of tandem mass spectrometry assays for Krabbe disease using dried blood samples.\(^6,7\) This method has been used for routine newborn screening by the state of New York (USA), since 2006.\(^8\) Two other states, Illinois and Missouri, have recently begun newborn screening for Krabbe disease.\(^9\)
This review evaluates the evidence on diagnostic accuracy and cost-effectiveness of tandem mass spectrometry for Krabbe disease to inform policy decisions on adding this test to the heel-pick test already performed on newborns in Canada.

RESEARCH QUESTIONS

1. What is the evidence on the accuracy of newborn screening, using tandem mass spectrometry, for identifying Krabbe Leukodystrophy?

2. What is the cost-effectiveness of newborn screening for Krabbe Leukodystrophy?

3. What are the evidence based guidelines regarding newborn screening for Krabbe Leukodystrophy?

KEY MESSAGE

There was a lack of high-quality evidence regarding the accuracy of tandem mass spectrometry for the detection of Krabbe disease. None of the reviewed guidelines recommended newborn screening for Krabbe disease as a standard procedure. The additional cost of adding Krabbe disease to an existing panel of newborn screening using tandem mass spectrometry was estimated to be $U.S.2.50 per infant tested.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid EMBASE, EBSCO CINAHL, The Cochrane Library (2012, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and January 18, 2012.

Searches were supplemented by reviewing the bibliographies of key papers.

Selection Criteria and Methods

Two independent reviewers screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance using a predefined checklist (Appendix 1). Any discrepancies between reviewers were discussed until consensus was reached. Full texts of any relevant titles/abstracts were retrieved, and assessed by two independent reviewers based on the initial inclusion criteria (Appendix 2). Any disagreement between reviewers was discussed until consensus is reached.
Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>All newborns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Newborn screening using tandem mass spectrometry</td>
</tr>
</tbody>
</table>
| Comparator         | - Any comparative diagnostic test (e.g. biochemical or molecular tests for diagnosis of Krabbe disease)  
|                    | - No screening |
| Outcomes           | - Diagnostic accuracy of newborn screening (i.e. sensitivity, specificity, positive predictive value, negative predictive value)  
|                    | - Costs of newborn screening  
|                    | - Cost-effectiveness (e.g. cost per case detected, cost per quality adjusted life year, cost per life year)  
|                    | - Recommendations on newborn screening for Krabbe disease |
| Study Designs       | Health technology assessments, systematic reviews and Meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, Canadian and international guidelines |

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, provided the results of a safety study, or presented preliminary results in abstract form. Duplicate publications and narrative reviews were also excluded.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was based on study design. The methodological quality of the included systematic review was evaluated using the measurement tool for the “assessment of multiple systematic reviews” (AMSTAR). AMSTAR is an 11-item checklist that has been developed to ensure reliability and construct validity of systematic reviews. For the included systematic review a numeric score were not calculated. Instead, the strengths and limitations of the study were described.

No randomized and non-randomized comparative studies were identified for critical appraisal. The methodological quality of the included diagnostic and cost-effectiveness studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool and guidelines for appraisal of economic studies by Drummond et al, respectively. The QUADAS tool is a 14-item questionnaire that is used to evaluate bias, data variability, and quality of reporting in diagnostic studies.

Guidelines were assessed for quality based on the scope, objectives, rigour of development and clarity of recommendations.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 231 potential citations were identified by the search in bibliographic databases, with 214 citations being excluded during the title and abstract review based on irrelevance to the
questions of interest. The full text documents of the remaining 17 articles were retrieved. Including the additional five additional articles that were found by the grey literature search and reviewing the bibliographies of the included articles, a total of 22 full text articles were reviewed. Of these 22 articles, 16 did not meet the eligibility criteria and were excluded, leaving six articles for this review.13-18 A PRISMA diagram demonstrating the study selection process is presented in Appendix 3.

Summary of Study Characteristics

Six articles that addressed at least one of the study questions were included in this review, consisting of one systematic review,15 two primary studies,13,17 and three guidelines.14,16,18

Four articles (including two guidelines) were published as journal articles,13-15,18 one as a doctoral dissertation document17, and one as a guideline document published by the National Academy of Biochemistry.16 All of the included studies were published in the United States of America.

The included systematic review and primary studies focused on the newborn screening for Krabbe disease, while all three guidelines targeted a broader spectrum of lysosomal storage disorders. Two of the guidelines were published by the American College of Medical Genetics.14,18 Both of the included primary studies were descriptive studies that reported on data from the New York State Newborn Screening program, however, data collection period varied for each study. One of the studies reported on both clinical and economic outcomes.17 The general characteristics of the included primary studies are summarized in Table 2.

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Study Design</th>
<th>Patient Characteristics (sample size)</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puckett, 201213</td>
<td>Retrospective chart review</td>
<td>Patients diagnosed with Krabbe disease by the Metabolic Division at CHOC Children's Centre (California, USA), between 2003 and 2008 (n=6)</td>
<td>Retrospective GALC enzyme activity test of dried blood spots obtained in routine newborn screening</td>
<td>GALC enzyme activity in leukocytes and GALC gene mutation analysis</td>
<td>Sensitivity of GALC enzyme test in newborn dried blood spots</td>
</tr>
<tr>
<td>Salveson, 201117</td>
<td>Cross-sectional diagnostic accuracy study</td>
<td>Newborns screened for Krabbe disease in New York State (USA) from August 2006 to July 2010. (n=1,062,000)</td>
<td>Newborn screening using GALC enzyme activity test of dried blood spots</td>
<td>GALC enzyme activity in leukocytes and GALC gene mutation analysis</td>
<td>Diagnostic accuracy* of GALC enzyme test in newborn dried blood spots Prevalence of Krabbe disease</td>
</tr>
</tbody>
</table>

Abbreviations: GALC= galactocerebrosidase; USA= United States of America
*diagnostic accuracy measurements included sensitivity, specificity, and positive and negative predictive values
Summary of Critical Appraisal

The strengths and limitations of included studies are summarized in Appendix 4.

The included systematic review\textsuperscript{15} included a comprehensive literature search of multiple databases and grey literature. The search was restricted to English-language publications. The articles were selected by two independent reviewers. Data was extracted by one reviewer, with a subset being extracted in duplicate. This review did not provide a summary of the included studies’ characteristics, and did not report on the quality of the included studies. Instead, a description of individual studies was provided in the article.

In neither of the included diagnostic studies comparator tests were performed independent of one another. Both studies used their reference standards for the individuals with a positive diagnostic test\textsuperscript{17} or confirmed Krabbe disease.\textsuperscript{13} Diagnostic accuracy of the test was reported in one of the studies.\textsuperscript{17}

The economic evaluation clearly stated the objective of the analysis and provided details on the subjects from whom cost estimates were obtained. Neither the form of the economic analysis nor the comparison group was stated by the author. Clinical effectiveness outcomes were not considered and no cost per outcome was estimated. Costs and clinical benefits from treatment arising from early detection of Krabbe disease were not considered.

All of the guidelines explicitly described their objectives and target populations. Systematic literature search methods were used in development of one guideline.\textsuperscript{18} The other two guideline documents either did not clearly explain their search methods,\textsuperscript{16} or used a non-systematic literature search.\textsuperscript{14} Recommendations were made by an expert panel in all three guidelines. Only one guideline graded the strength of the evidence used in development of recommendations based on the quality of evidence.\textsuperscript{16} One guideline used an explicit multi-criteria scoring system to determine the usefulness of newborn screening test in various lysosomal storage disorders, including Krabbe disease.\textsuperscript{18}

Summary of Findings

What is the evidence on the accuracy of newborn screening, using tandem mass spectrometry, for identifying Krabbe Leukodystrophy?

One systematic review and two primary studies addressed the accuracy of tandem mass spectrometry in diagnosis of Krabbe disease. A summary of the study findings and authors’ conclusions can be found in Appendix 5.

Systematic Review

Kemper et al. (2010) conducted a systematic review of evidence published from 1988 to 2008 to evaluate the evidence regarding screening, diagnosis and treatment of Krabbe disease.\textsuperscript{15} Of the 13 studies included in this review, six studies addressed tandem mass spectrometry as a potential newborn screening test for Krabbe disease.\textsuperscript{6-8,19-21} Four of these six articles were descriptive studies reporting daily mean activity levels of GALC enzyme in patients with Krabbe disease, or laboratory techniques to detect enzyme products using tandem mass spectrometry.
Two studies reported on the New York State newborn screening experience.\textsuperscript{6,19}

A report by Duffner et al.\textsuperscript{8} described the process used in this program, from screening to confirmation of diagnosis. This report was based on the data which had been collected from approximately 550,000 newborns by the end of June 2008. The screened newborns were re-tested if the daily mean GALK activity was less than 20%. If the average of GALK daily mean activity of three samples from the same dried blood spot was less than 8%, the newborn was considered as screen-positive, regardless of the results of the subsequent genetic test. Daily mean enzyme activity levels between 8% and 20% required a confirmation using molecular testing. Of the 550,000 screened newborns, 25 were reported to have positive screening results. Among screen-positive infants, four were considered to be high risk for early infantile Krabbe disease. Two of the high risk infants underwent stem-cell transplantation, one of whom died from the complications of the procedure.\textsuperscript{8}

The authors of the systematic review did not calculate the diagnostic accuracy measures of the screening test, due to diagnostic challenges and lack of sufficiently long-term follow-up data for both screen-positive and screen-negative newborns. They believed that the New York State experience had shown the feasibility of the newborn screening program for Krabbe disease, however, longer term follow up was needed to prove the effectiveness of the program.

**Primary Studies**

Puckett et al. (2012)\textsuperscript{13} retrospectively reviewed the newborn screening cards of five patients diagnosed with early infantile Krabbe disease between 2003 and 2008 and one additional patient with late onset disease. The newborn screening cards, including dried blood spots from routine newborn screening, had been stored for 1.4 to 13.5 years in the Metabolic Division of CHOC Children’s Centre (Orange, California). GALK activity was retrospectively measured on these samples and the results were interpreted based on the New York State Newborn Screening criteria (see the previously described systematic review\textsuperscript{15} for details). In addition, tests for GALK enzyme in leukocytes and gene mutation tests were performed in all six patients. The activity of GALK enzyme in newborn dried blood samples of all six patients was below 20% of the daily mean. Based on these results the authors suggested GALK enzyme analysis in newborn dried blood spots as a highly sensitive test.

As a part of her doctoral thesis work, Salveson (2011) evaluated the diagnostic performance of the newborn screening test for Krabbe disease using the data collected from New York State newborn screening program between August 2006 and July 2010.\textsuperscript{17}

The author used the data from the State annual reports of nine positive newborn screening results to calculate diagnostic accuracy. Overall, data from 1,062,000 newborns were available. Newborns were considered as screen-positive if the mean activity of the GALK enzyme from dried blood sample was 12% or less, and screen-negative if the mean activity was more than 12%. Confirmatory GALK enzyme testing and molecular tests were used as the gold standard in screen-positive newborns. The diagnosis was confirmed if the patient had an enzyme level equal to or lower than 0.15 mmol/hour/mg protein along with a genetic test demonstrating GALK gene mutation. Enzyme levels greater than 0.16 mmol/hour/mg protein with or without a positive genetic result were considered negative (no disease). In screen-negative newborns, clinical diagnosis in later stages of life was used to determine false-negative results of screening.
Based on the available data, sensitivity was calculated at 100%, and specificity was 99%. The prevalence of Krabbe disease in this study population was approximately 1 per 100,000 births; and positive and negative predictive values were calculated at 5% and 100%, respectively. Criticizing the State reports for not including the 19 newborns with low enzyme activity and mutations that could develop into later onset forms of Krabbe disease, Salveson repeated the calculation after addition of those 19 infants. Sensitivity, specificity, and negative predictive value remained unchanged; however, positive predictive value rose to 15%, as a result of increased prevalence (2.6 per 100,000 births).  

What is the cost-effectiveness of newborn screening for Krabbe Leukodystrophy?  

No primary cost-effectiveness studies of newborn screening for Krabbe disease were found for this review. However, an evaluation of the costs associated with newborn screening was conducted as part of a doctoral dissertation. This study used data from the New York newborn screening program, which added Krabbe disease to their screening panel in 2006. The dissertation stated that the cost of adding Krabbe disease to the newborn screening panel was $2.50 per test. Personal communication from 2009 was cited as the source of this cost. The costs associated with confirmatory testing and evaluations after infants are diagnosed as positive for Krabbe disease from their newborn screening test were also assessed. Using data from New York State, the average costs of confirmatory testing was estimated average $U.S.1,475 per infant screened positive for Krabbe disease. These costs included DNA analysis for both parents and the infant, a confirmatory enzyme test for the infant, venipuncture, and a consultation by a metabolic specialist. Additional evaluation costs for infants with a positive confirmatory test were estimated average $U.S.2,669. These costs included hospital admission, a neurology consult, a nerve conduction study, a brainstem auditory evokes response study, and an MRI with and without contrast. A specific reference year for the costs was not provided. However, it is reported that these costs are represent those incurred between 2006 and 2010. The author concluded that studies are needed to assess the costs of Krabbe disease from a societal perspective and that it should include the costs of treatment and follow-up.  

An estimate of the cost per outcome of Krabbe disease screening was not provided. However, the cost per case of Krabbe detected can be estimated using data on the prevalence of Krabbe disease and diagnostic accuracy of the screening test. Based on results from over a million newborn screening tests in New York State, the dissertation author estimated the prevalence of Krabbe disease to be 2.6 per 100,000 infants. The sensitivity of the screening was estimated to be 100%. Based on this data along with the cost per screening test, the cost per Krabbe case detected using newborn screening can be estimated to be $96,154 ($2.50/0.000026). If the cost of confirmatory tests and the false positive tests reported in the dissertation are considered, the cost per case detected can be estimated to be $108,656. It is difficult to judge whether this would be considered to be cost effective as it does not take the costs, the mortality benefit or the quality of life impact of early treatment of Krabbe disease.  

What are the evidence based guidelines regarding new born screening for Krabbe Leukodystrophy?  

Three guideline documents addressing tandem mass spectrometry for Krabbe disease were identified. A summary of the included guidelines is provided in Appendix 6.
In the guideline published in 2011 by the American College of Medical Genetics (ACMG) Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases, Krabbe disease is listed among several genetic disorders for which newborn screening is possible using the same dried blood sample. In this guideline document, that was developed through the review of English language literature and consensus development, assessment of GALC enzyme levels in white blood cells and molecular analysis of the GALC gene were recommended for diagnosis of Krabbe disease. Newborn screening using tandem mass spectrometry was not included as a standard diagnostic strategy for this disorder, although the recent use of this technology in New York State was briefly discussed.

In 2009, the National Academy of Clinical Biochemistry (NACB), a scientific academy affiliated with the American Association for Clinical Chemistry, published a laboratory medicine practice guideline to evaluate the role of expanded newborn screening programs using tandem mass spectrometry. The recommendations of this guideline were made by a panel of experts based on relevant evidence published in the medical and scientific literature, and guidelines produced by other medical academic groups, such as the American College of Medical Genetics and the Centers for Disease Control. This guideline listed Krabbe disease among the 22 conditions that are detectable by tandem mass spectrometry, but are not identified by the expert panel as primary target conditions for routine newborn screening, due to “less strong” evidence.

In 2006, the ACMG Task Force, 2006, conducted a systematic review of scientific literature on the effectiveness of newborn screening programs. The identified evidence was used by an expert panel to develop recommendations on newborn screening for 84 specified conditions. A number of these conditions were included in the existing routine newborn screening, and others were being considered for addition to existing routine screening tests. To develop a scoring system the Task Force used 19 criteria included in one of the following three categories: clinical characteristics of the disorder, analytical characteristics of the screening test, and diagnosis, management and treatment of the disorder. As a result a scoring system with a maximum of 2100 points was developed. The Task force did not consider the conditions scoring below 1000 appropriate for screening, the conditions with scores ≥1200 were considered appropriate for newborn screening, and the conditions that scored between 1000 and 1199 were considered as secondary targets for screening. Based on these decision criteria, the ACMG guideline provided a list of 29 disorders for screening, with an additional 25 secondary target conditions. Krabbe disease which acquired a total score of 447 (44 respondents) was not in this list.

Limitations

The main limitation of this review is the lack of high quality studies to assess the diagnostic accuracy of tandem mass spectrometry for newborn screening of Krabbe disease. Only one study formally estimated the diagnostic accuracy of the screening test. A strength of this study was that the estimates of test characteristics was based upon a large number of screening tests (over 1 million). However, the number of true positive and false negative patients was not based on clinically confirmed cases of Krabbe disease. Instead the number of true positive patients and false negative patients were based on patients considered to be at moderate or high risk of developing Krabbe disease based on a confirmatory enzyme test. Another limitation is that evidence of the effectiveness of early treatment of Krabbe disease resulting from newborn diagnosis was not considered as this was beyond the scope this review. Additionally, no formal cost-effectiveness analysis of newborns screening were identified. One analysis of the costs of adding Krabbe disease to an existing newborn screening program was found. This analysis was
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Although it had limitations, a study based on the New York State newborn screening program estimated tandem mass spectrometry to have both high sensitivity and specificity for the early diagnosis of Krabbe disease in newborns. The decision as to whether to add testing for Krabbe disease in existing newborn screening panels may consider aspects beyond diagnostic accuracy of the test. These include the costs of the additional screening as well as the benefit of early identification of the disease. The cost of adding Krabbe disease testing to an existing screening regimen was estimated to be $U.S.2.50 per infant in New York State, however this could have a significant impact on a hospital budget as it would be used for all newborns. Since the goal of early screening of Krabbe’s disease is initiation of early treatment, the benefit of available treatment options may also be considered when deciding of whether to add Krabbe disease testing to newborn screening panels. None of the reviewed guidelines recommended newborn screening for Krabbe disease as a standard procedure.
REFERENCES


Appendix 1: Title and abstract screening checklist

Reviewer: 
Date: 
Ref ID: 
First Author (year): 

| 1 What is the STUDY POPULATION in this article? | □ newborns (include)  
□ All other population (exclude) |
| 2 What is the INTERVENTION? | □ Newborn screening using tandem mass spectrometry (include)  
□ Any other interventions (e.g. other screening or diagnostic tests (exclude)  
□ Can’t decide (include) |
| 3 What is the TYPE OF STUDY reported in this article? | □ Report of a clinical trial (controlled/uncontrolled; randomized/non-randomized) (include)  
□ Meta-analyses/systematic reviews/HTAs (include)  
□ Report of a prospective or retrospective cohort study (include)  
□ Report of a case-control study (include)  
□ Report of a before-after study (include)  
□ Report of an analytical cross-sectional study (include)  
□ Academic/narrative review, comment, editorial, letter, note, patient handout, study design description (exclude)  
□ All other study designs (exclude)  
□ Can’t decide (include) |

Selection decision: 
□ Include  
□ Exclude
Appendix 2: Full text screening checklist

Reviewer:  Date:  
Ref ID:  First Author (year):

1. Did this article include newborns who underwent screening for Krabbe disease using tandem mass spectrometry?
   - Yes (include)
   - No (exclude)
   - Maybe (include)

2. Is the article the PRIMARY REPORT of the FINAL results from:
   - Report of a clinical trial (controlled/uncontrolled; randomized/non-randomized) (include)
   - Meta-analyses/systematic reviews/HTAs (include)
   - Report of a prospective or retrospective cohort study (include)
   - Report of a case-control study (include)
   - Report of a before-after study (include)
   - Report of a cross-sectional study (include)
   - All other study types (exclude)
   - Can't decide (include)

3. What COMPARATOR is used in the study?
   - Any comparator, including no screening (include)
   - No comparator (include)

4. Include if the OUTCOME of interest in the study is one of the following:
   - Diagnostic accuracy of newborn screening (i.e. sensitivity, specificity, positive predictive value, negative predictive value) (include)
   - Costs of newborn screening (include)
   - Cost-effectiveness (e.g. cost per case detected, cost per quality adjusted life year, cost per life year) (include)
   - None of the above (exclude)

5. Final Decision
   - Include
   - Exclude
   - Non-English /Unable to translate

Reason for Exclusion:
   - Inappropriate study population
   - Not study types of interest
   - Not primary report of study
   - Study description only
   - No intervention of interest
   - Inappropriate control group
   - No relevant outcomes
Appendix 3: Selection of Included Studies

231 citations identified from electronic literature search and screened

214 citations excluded

17 potentially relevant articles retrieved for scrutiny (full text, if available)

5 potentially relevant reports retrieved from other sources (grey literature, hand search)

22 potentially relevant reports

16 reports excluded:
- irrelevant population (2)
- irrelevant comparator (1)
- irrelevant outcomes (6)
- irrelevant study design (1)
- already included in the selected systematic review (1)
- Other (review articles, study description, duplicate reports) (5)

6 reports included in review:
  Systematic review (1)
  Diagnostic studies (2)
  Guidelines (3)
### Appendix 4: Critical Appraisal of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews</strong></td>
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</table>
| Kemper, 2010                          | • Comprehensive literature search based on pre-defined criteria.  
• Inclusion of grey literature  
• Duplicate study selection  
• Sources of study support were clearly acknowledged. | • Summary of study characteristics and list of included and excluded studies was not provided.  
• Scientific quality of the included evidence was not assessed. |
| **Descriptive Studies**                |           |             |
| Puckett, 2012                         | • All patients received the same diagnostic tests. | • The study population consisted of individuals with confirmed disease  
• The diagnostic test (enzyme activity from dried blood spot) was performed on the screening samples that were stored for a long time period. |
| Salveson, 2011                        | • Patients were representative of those who would receive the test.  
• Execution of index tests was described in sufficient detail to permit replication of the test  
• The results of the diagnostic test were interpreted without knowledge of the results of the reference standard. | • The reference standard was used for screen-positive individuals. The accuracy of the test in screen-negative individuals was based on presence of clinical symptoms in later stages of life. |
| **Cost-effectiveness Analysis**       |           |             |
| Salveson, 2011                        | • Research question is stated.  
• Details of subjects that costs were based on are provided | • Type of economic evaluation not formally stated, though implied to be cost minimization analysis  
• Comparator is not stated, though implied to be absence of Krabbe newborn screening program  
• Cost per outcome not calculated  
• Costs from treatment once newborns are diagnosed with Krabbe disease not incorporated  
• A specific reference year for costs not stated. |
| **Guidelines**                        |           |             |
| Wang, 2011                            | • Clinical questions, objectives, target population, and target audience of the guideline were explicitly described.  
• Methods used for formulating the recommendations were clearly described  
• Key recommendations are identifiable. | • Non-systematic (targeted) search of literature by the expert panel members.  
• Criteria for inclusion and exclusion were not described.  
• Recommendations were made by an expert panel based on a non-systematic (targeted) search of literature and personal experience  
• Level of evidence supporting the |
<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Bennett, 2009<sup>16</sup>             | • Clinical questions, objectives and target population of the guideline were explicitly described.  
• Recommendations were made by an expert panel  
• The strength of recommendations was graded based on the quality of evidence.  
• Key recommendations are easily identifiable  
• Level of evidence supporting the recommendations is explicitly stated. | • It is not clear whether systematic methods were used to search for evidence.  
• Criteria for inclusion were not clearly described  
• Methods used for formulating the recommendations were not clearly described |
| Watson, 2006<sup>18</sup>              | • Clinical questions, objectives and target population of the guideline were explicitly described.  
• Systematic methods were used to search for evidence  
• Inclusion and exclusion criteria were clearly described.  
• Recommendations were made by an expert panel using a standard multiple-criteria scoring tool.  
• Methods used for formulating the recommendations were clearly described | • Level of evidence supporting the recommendations is unclear. |

Abbreviations: GALC = galactocerebrosidase; USA = United States of America  
<sup>*</sup>diagnostic accuracy measurements included sensitivity, specificity, and positive and negative predictive values
## Appendix 5: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kemper, 2010&lt;sup&gt;15&lt;/sup&gt;</td>
<td>One of the included studies reported on data collected from 550,000 newborns screened the New York State. Of 25 infants with positive screening results, four were considered to be high risk for early infantile Krabbe disease. Two of the high risk infants underwent stem-cell transplantation, one of whom died from the complications of the procedure.</td>
<td>Diagnostic accuracy measures of the screening test were not calculated, due to diagnostic challenges and lack of sufficiently long-term follow-up data.</td>
</tr>
<tr>
<td><strong>Descriptive Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puckett, 2012&lt;sup&gt;13&lt;/sup&gt;</td>
<td>The activity of GALC enzyme in newborn dried blood samples of all six patients was below 20% of the daily mean.</td>
<td>GALC enzyme analysis in newborn dried blood spots as a highly sensitive test.</td>
</tr>
<tr>
<td>Salveson, 2011&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Of 1,062,000 infants screened for Krabbe disease 4 newborns with early-infantile form of the disease were identified. Twenty four infants were identified with low enzyme activity and mutations that may cause later onset forms of the disease. Sensitivity = 100% Specificity = 99%. Positive predictive value = 5% Negative predictive value =100%, prevalence = 1 per 100,000 births</td>
<td>The screening test is highly sensitive and specific. However, newborns may be diagnosed with a disease that may not show symptoms until adulthood.</td>
</tr>
<tr>
<td><strong>Cost-effectiveness Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salveson, 2011&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Additional cost of adding Krabbe disease to current newborn screening program was $U.S.2.50 per test. Average cost of confirmatory testing related cost for each infant diagnosed as positive in newborn screening averaged $U.S1,475. Average cost for evaluation diagnosed as positive through confirmatory testing averaged $U.S.2.669</td>
<td>The cost of the program from the perspective of the state of New York is not excessive. Studies are needed to assess the costs of Krabbe disease screening from the societal perspective and should include treatment and follow-up costs.</td>
</tr>
</tbody>
</table>
## Appendix 6: Summary of the included guidelines

<table>
<thead>
<tr>
<th>Guideline, Year [publishing organization]</th>
<th>Objectives</th>
<th>Audience</th>
<th>Foundation of the recommendations</th>
<th>Recommendation (level of evidence, when available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2011 [ACMG]</td>
<td>● To provide guidance for confirmatory testing and subsequent management of selected lysosomal storage diseases (including Krabbe disease) in pre-symptomatic individuals</td>
<td>Health care providers, including metabolic disease specialists, biochemical geneticists, and neuromuscular experts.</td>
<td>Literature review Expert opinion Consensus development</td>
<td>● The diagnosis of Krabbe disease should be confirmed by: 1) Measuring GALC in leukocytes; and 2) GALC gene mutation analysis.</td>
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<td>Bennett, 2009 [NCCB/AACC]</td>
<td>● To evaluate the data supporting the role of expanded newborn screening metabolic disorders using tandem mass spectrometry,  ● To determine optimal methods and performance characteristics for performing the testing, and for optimizing confirmatory follow-up testing procedures for positive screens.</td>
<td>Clinical and laboratory practice decision makers</td>
<td>Literature review, Review of the surveys and guidelines produced by other medical academic groups and organizations, including ACMG and CDC. Expert opinion</td>
<td>No recommendations related to the use of newborn screening for identifying Krabbe disease, due to the lack of evidence to show clinical benefit of early newborn diagnosis of Krabbe disease. Krabbe disease was listed as a Lysosomal storage disorder that “can be diagnosed by tandem mass spectrometry”.</td>
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<td>Watson, 2006 [ACMG]</td>
<td>● To define responsibilities for collecting and evaluating outcome data, including a recommended uniform panel of conditions to include in state newborn screening programs.</td>
<td>Newborn screening programs in the United States</td>
<td>Systematic literature review Expert opinion Consensus development using a multi-criteria scoring system</td>
<td>No recommendation for the use of newborn screening for identifying Krabbe disease  ● The expert panel identified – 29 conditions for which screening should be mandated (core panel); and – 25 secondary conditions (e.g. conditions that were part of the differential diagnosis of a condition in the core panel, or were clinically revealed with screening technology but no efficacious treatment existed)</td>
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Abbreviations: AACC= American Association for Clinical Chemistry ACMG= American College of Medical Genetics; CDC= the Centers for Disease Control; GALC= galactocerebrosidase; NCCB= National Academy of Clinical Biochemistry