Published in final edited form as:

Dev Disabil Res Rev. 2011 ; 17(1): 15–18. doi:10.1002/ddrr.133.

Dangerous and expensive screening and treatment for rare childhood diseases: the case of Krabbe disease

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Abstract

Public policy surrounding newborn screening is in flux. New technology allows more screening for more diseases at lower cost. Traditional criteria for target diseases have been criticized by leading health policymakers. The example of newborn screening for Krabbe disease highlights many of the dilemmas associated with population-based screening programs. Krabbe is difficult to diagnose, variable in its natural history, and does not always respond to treatment. The only available treatment is hematopoietic stem cell transplantation, which is expensive, risky, and of uncertain efficacy. This paper analyzes the debate about Krabbe as an example of the sorts of debates that will likely arise for many more diseases over the next decade. I conclude that pilot programs in pioneer states should be carefully evaluated before testing for Krabbe is universalized.

Keywords

newborn screening; lysosomal storage disease; Krabbe; cost-effectiveness; ethics

There are many dilemmas associated with innovative, potentially dangerous, and expensive treatments for rare and debilitating childhood diseases. First, there is the risk-benefit ratio. New treatments inevitably have unknown risks. That is why we study them carefully. The uncertainty about relative risks and benefits creates tension between our natural and justifiable desire to save children and our justifiable fear that experimental approaches to screening, diagnosis and treatment will do more harm than good. There is a haunting fictional portrayal of such an outcome in Camus' novel, *The Plague*, in which the physician-scientist, Dr. Castel, tries an experimental antiserum on a child. It merely prolongs the child's agonizing final hours, "For moments that seemed endless he stayed in a queer, contorted position, his body racked by convulsive tremors; it was as if his frail frame were bending before the fierce breath of the plague, breaking under the reiterated gusts of fever."¹

A second sort of dilemma arises if an experimental therapy turns out to be only partially successful and, instead of providing a cure or a successful long-term treatment, is in the case of thyroid hormone for congenital hypothyroidism, it only slows the progression of the disease. In such cases, screening, diagnosis and treatment might save children's lives, only to leave them with severe lifelong impairments. This situation does not only arise in the context of rare diseases. It has been an ongoing concern in other areas of pediatrics, such as

neonatal intensive care for babies born at the borderline of viability. Both of these two concerns ultimately become part of cost-benefit analysis. If screening, diagnosis and treatment programs are expensive and lead to unsatisfactory outcomes, they can be criticized as an inappropriate allocation of scarce societal resources. These concerns raise issues of justice, efficiency, and the opportunity costs associated with expensive and marginally successful programs. Since we never have enough money, we should try to spend it where it will do the most good.

Newborn screening for Krabbe disease as a paradigm case

Newborn screening for Krabbe disease illustrates all of these dilemmas. The disease is rare but devastating, the screening program is costly, the natural history of the disease is not well understood, and the only available treatment – hematopoietic stem cell transplantation – is expensive and risky.

How does screening for Krabbe work?

Krabbe disease, also referred to as globoid cell leukodystrophy, causes a deficiency in galactocerebrosidase (GALC), the enzyme responsible for preventing a build up of galactolipids in the brain. Without the regulation of galactolipids, the growth of the myelin sheath around nerve cells is severely impaired. Krabbe disease usually presents in the first 6 months of life, with symptoms such as loss of muscle tone, spasticity, irritability, seizures, and loss of head control, hearing, and sight. A child in the later stages of Krabbe disease is immobilized and has reducing levels of responsiveness and brain activity. Most die before age 2. The younger the child is at the age of diagnosis, the faster the disease progresses.² The only potentially effective treatment for Krabbe disease is hematopoietic cell transplant. This has generally been done using umbilical cord blood. In 2005, Escolar et al reported the results of a study of the efficacy of umbilical cord blood transplantation for Krabbe disease. They compared outcomes for eleven infants who were transplanted before the onset of symptoms to outcomes for 14 infants who were transplanted after the development of symptoms. They reported that “Infants who underwent transplantation before the development of symptoms showed progressive central myelination and continued gains in developmental skills, and most had age-appropriate cognitive function and receptive language skills, but a few had mild-to-moderate delays in expressive language and mild-to-severe delays in gross motor function. Children who underwent transplantation after the onset of symptoms had minimal neurologic improvement.”³

This description of the natural history of Krabbe disease and of the possibility of successful treatment would make it seem like an ideal target for a population-based newborn screening program. However, the story is a little more complicated. Screening programs are designed to identify the gene that is associated with Krabbe disease. But not all children who carry the gene actually develop the disease. Thus, the screening program and the confirmatory tests that follow allow the identification of a population that is “at risk” of developing Krabbe, rather than a population that is destined to develop the disease. Those children must then be followed carefully in order to determine when and whether they show early symptoms of the disease.

Thus, screening and diagnosis of Krabbe disease is a complex and expensive undertaking. It requires three stages. First, newborn blood spots are analyzed using tandem mass spectrometry. Those that screen positive are sent for DNA testing to determine if they have a mutation in the GALC gene. Finally, those with positive blood spot results and positive DNA analysis are analyzed for galactocerebrosidase activity. Based on the level of galactocerebrosidase activity, they are then categorized as being at high, medium or low risk of actually developing the disease. Those with the lowest levels are at highest risk of becoming symptomatic, while those with higher levels of enzyme activity are at lower risk. The incidence of clinically symptomatic Krabbe is slightly lower than previously thought: 0.26 cases per 100,000 instead of 0.9 cases per 100,000.

Screening for Krabbe disease is complex and expensive. What is the experience in New York State

In 2006, the state of New York became the first state to initiate a newborn screening program for Krabbe. Since then, over a million children have been tested. In 2010, Kemper et al described New York's experience with the first 550,000.⁴

New York's program has increased our understanding of the complexity of Krabbe disease and, by implication, of other lysosomal storage diseases. As with many screening programs, there were some surprises. First, they found that population screening yielded different estimates of the prevalence of disease than prior estimates. Prior to the newborn screening programs, Krabbe disease was thought to affect 1:100,000 newborns in the U.S. In the newborn screening program in New York, however, the rate of positive tests was 5:100,000. Many of the children who screened positive, however, were asymptomatic.

Second, New York realized that not everyone with a positive test had symptoms of the disease. They implemented a program to follow such children clinically. They are tested every child every three months during the first year of life. Testing consisted of neurologic examination, MRI, lumbar puncture, audio and visual evoked response tests, and nerve conduction studies. These tests resulted in a composite risk score.

Children would be referred for transplantation if they had a combination of abnormal neurologic exam, abnormal MRI, increased cerebrospinal fluid protein or abnormalities on other tests.⁵ All children in the New York program were to be followed, including those who received a transplant and those who did not. This database should allow evaluation of the efficacy of the screening program, including the program of periodic clinical evaluation of children who test positive but who remain asymptomatic.

Of the 25 babies in New York who have screened positive, only 2 have developed symptoms of Krabbe disease. This gives the screening test a positive predictive value of 8%. Both of the positive children who developed symptoms received a transplant. One died. The other child did not develop any further symptoms of Krabbe but was reported to be "developmentally delayed." Kemper et al concluded, "Diagnosing affected infants identified by newborn screen from a general population is particularly challenging. Children who have screened positive require repeated and sometimes invasive testing to confirm or rule out a

diagnosis. No peer-reviewed published information is available regarding the completeness of this follow-up or the impact of follow-up on families.”⁶

Part of the challenge in such a screening program is to decide how to interpret test results in order to determine with reasonable certainty which infants actually have the disease. The presence of children who screen positive but who remain asymptomatic has led to some difficult choices for doctors, parents and policy makers. The stakes are high. Those who have the disease may benefit from an early stem cell transplant. Such transplants, however, are risky.. The mortality rate after a hematopoietic stem cell transplant is 5–10% Another 10% of patients will develop severe graft-versus-host disease. The outcomes for any particular child may be altered by the histocompatibility factors of the donor bone marrow. In Krabbe, transplants need to be done early if they are to succeed, so the pressure to monitor and diagnose early neurologic symptoms is intense. Any child whose transplant is delayed will have a worse outcome than they might have had with an earlier transplant. But those who do not have the disease will be harmed by undergoing a transplant.

What do we know about cost-effectiveness?

There have been no published cost-effectiveness analyses of newborn screening for Krabbe. There are, however, many analyses of other newborn screening programs. They generally conclude that such screening programs are cost-effective.⁷ Some of these analyses focus on screening for a specific disease. Others examine the overall cost-effectiveness of expanding the number of tests on the newborn screening panel. Examples of the former are studies by Haas et al.⁸ and van der Hilst et al⁹ of screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia and the Netherlands. Examples of the latter include studies by Schulze et al¹⁰ and by Feuchtbaum and Cunningham¹¹ on screening programs in Germany and in California that used tandem mass spectrometry (MS/MS). Both concluded that expanded screening panels were cost-effective. Schulze et al estimate that each test costs seven dollars, that 1:4100 infants test positive, and that most benefit from early diagnosis. Thus, “costs would be quickly offset by the reduction of expenses for hospitalization and medications...for a patient with an inborn error of metabolism not diagnosed and treated in a timely fashion.” Interestingly, they don’t include in their analysis the cost of false positive tests or the cost of treatment that doesn’t cure the underlying disease. Their model is based on screening for disease for which there is a relatively cheap, safe, and effective treatment. Feuchtbaum and Cunningham, similarly, conclude, “We found that the benefits of MS/MS screening outweighed the costs and that the net benefits were significant and robust in various scenarios with various conservative underlying assumptions.” Their analysis was a little more comprehensive than that of Shulze, and included scenarios that modeled differed levels of treatment effectiveness.

None of these cost-effectiveness studies examine situations comparable to the current situation with Krabbe disease. In that situation, the testing is more expensive than is testing for most other newborn diseases. In addition, the treatment is more expensive and less effective than treatment for many other diseases that are diagnosed by newborn screening.

The only analysis of the costs (but not the benefits!) of the New York experience is an unpublished doctoral thesis by Salveson that is available on the internet (<http://>

academiccommons.columbia.edu/catalog/ac:132317). Salveson reports, “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.” This does not include the cost of the confirmatory follow-up testing that is not covered by the state. The average cost to families was \$2700, some of which was covered by insurance. They estimated that the total cost of testing was \$500,000 and \$750,000 per case of disease diagnosed. That did not include the cost of the treatment that those who were diagnosed would need. Thus, Krabbe screening is more expensive than many other screening programs (\$11M to screen from 29 diseases), but it is not different by orders of magnitude. It is simply at the high end of costliness. Most other diseases, however, either have simple and effective treatments or no treatment at all. If one combines the cost of screening for Krabbe with the cost of treatment and the uncertain outcomes after treatment, the cost-effectiveness analysis becomes more complex. At this point, there isn’t enough data to actually calculate a dollar figure for cost-effectiveness.

This has led to debate. At a meeting reported by the newspaper, *Neurology Today*, two neurologists argued about the value of Krabbe screening. Jennifer Kwon, from University of Rochester, argued that the costs weren’t worth it. Nigel Banford, from University of Washington, responded, “There is always a cost consideration, but there is a humanity component as well. If you can rescue a child with a stem cell transplant or other therapies, what a difference that would make to that particular baby and family.”¹²

Debates about cost-effectiveness are mired in a set of irresolvable internal tensions that allow different conclusions to be drawn from the same data. The central question is this: what is the value of a life saved? From that question, one can spin off other derivative questions. How should the value of a life be adjusted for quality of life? Are there measures that we can all agree upon to assess the quality of life in a quantitative, objective, and standardized way? Without such measures, cost effectiveness studies must either exclude any considerations of the impairment in their assessments, or they must assign a dollar value to those impairments. Either approach is problematic, the former because it doesn’t reflect the way most people think about the value of medical treatments, the latter because it devalues the lives of people with disabilities.

More importantly, cost-effectiveness analysis are unlikely to be the determining factor in decisions about whether or not to implement programs to screen and treat for rare but devastating diseases. Because the diseases are rare, many of the individual children and families who suffer will be identifiable. It is difficult to deny treatment to identifiable children, no matter how expensive the treatment may be. In the end, cost-effectiveness analysis may indicate just how much we are willing to pay to save the life of a child with Krabbe disease, but they will not persuade anyone about the wisdom of screening or treatment decisions. Those decisions will be driven by emotional factors, political alliances, and moral commitments, rather than underlying costs.

What do parents think?

If cost is not the driving factor, then decisions will likely be driven by the sentiments of citizens – that is, of voters – who participate in these programs. Thus, we might ask whether parents and pediatricians find the programs helpful or harmful,

Answers to these questions come from qualitative research Salverson interviewed parents whose children tested positive. She reports that most parents were glad to have gotten the information. One parent said, "... 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." Another parent said, "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." Salverson concludes that "Parents were generally supportive of KD screening, and satisfied they knew important information about their child's health." (<http://academiccommons.columbia.edu/catalog/ac:132317>, p 77.)

Such sentiments by parents, along with the enthusiasm of many doctors and politicians, along with further advances in screening technology all suggest that, in the future, we will see more such screening and treatment programs, not less. This juggernaut of science and politics will create challenges for practicing pediatricians, who must become more knowledgeable about these new tests in order to guide parents through the complicated decisions surrounding newborn screening.

The Future of Newborn Screening. Broadly speaking, there are two ways of analyzing the appropriateness of newborn screening for any particular disease or condition. One view, that might be called the "classic view," is that screening should only be done for diseases that can be treated with proven treatments that are affordable and readily available to all children who are identified by the screening program. This approach evolved out of principles that were famously articulated by Wilson and Jungner in a report that they did for the World Health Organization in 1968.¹³

Recently, some leading scientists and policy makers have challenged the classic view and argue that screening is appropriate even for diseases for which there is no proven treatment available. In such cases, screening has many other purposes. It gives parents diagnostic and prognostic information about their child. It allows parents to make more informed reproductive decisions in the future. In some cases, it may allow research on new treatments for previously untreatable diseases.

Proponents of the classic view include a group of leading pediatric bioethicists who recently warned clinicians, parents and policy makers to "proceed with caution."¹⁴ They warn of the dangers of expanded screening, including the problem of dealing with false-positive results, the lack of a service-delivery infrastructure to care for children who are diagnosed by screening programs, and the legal and ethical issues associated with mandating dozens of new tests. They note that "population screening of asymptomatic individuals is rarely an

effective approach to uncommon diseases.” They advocate more research on the efficacy of the testing programs. They note, “By pooling data on a regional or national basis, information could be acquired on program benefits, harms, and costs with a sufficient number of affected children to inform newborn screening policy decisions.” They cite historical examples of situations in which expensive screening programs led to more harm than good., including early screening programs for PKU, sickle cell disease, and neuroblastoma.¹⁵ Instead, these screening programs revealed how little we had understood about the natural history of this childhood cancer.

Opponents of the classic view argue for a new paradigm in evaluating new born screening. Duane Alexander, former head of the National Institute for Child Health and Development, argues that newborn screening programs should be expanded beyond situations that meet the Wilson-Jungner criteria in order to identify as many children with congenital diseases as possible. He acknowledges that, for many such children, there is no currently available treatment. However, he thinks that only through screening will we be able to identify such children and be able to develop new treatments for the. He proposes that we should screen for as many conditions as possible, “including genetic metabolic disorders (especially those associated with mental retardation or neurodegenerative diseases), immunodeficiency disorders, muscular dystrophies, cystic fibrosis, hemoglobinopathies, coagulopathies, and genetic deafness syndromes.”¹⁶ His hope is that such screening will become the basis of national registries and that those registries would enable research on innovative treatments for many diseases for which no treatment is currently available. In advocating for such an approach, he explicitly rejects the conventional wisdom that has guided such screening programs for the last forty years, the idea that screening programs should only focus on diseases for which effective treatments are currently available. Alexander calls this cautious approach an outmoded dogma that “dooms us to continued ignorance and unavailability of treatment because affected individuals are not identified until they exhibit symptoms, too late for effective preventive interventions to be tested or applied.”

This tension between gung-ho, optimistic scientists and nay-saying, doom-and-gloom bioethicists is a constant feature of the cultural politics of medical innovation today. Scientists tend to see the potential benefits of innovation while ethicists see the potential risks.

For today, Alexander’s arguments seem to have prevailed over those of the bioethicists. Most developed countries have expanded the panel of diseases for which routine newborn screening is now done beyond those that meet Wilson-Jungner criteria.¹⁷¹⁸¹⁹ That, of course, does not mean that such programs will ultimately be beneficial or that the ethicists’ warnings can be ignored. Only time, and data, will answer that question. For today, Krabbe disease screening, diagnosis and treatment is at the cutting edge of such debates. It is the most controversial newborn screening test in widespread use today. New York State has a program up and running. Illinois and Missouri are about to start newborn screening for Krabbe. Policy makers around the country will watch these vanguard states closely to determine whether the programs are effective, whether they can be implemented as a reasonable cost, and whether children actually benefit from early treatment.

Acknowledgments

Grant Support: This work

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