# Case Discussion

# The Ethics of Krabbe Newborn Screening

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The experience of newborn screening for Krabbe disease in New York State demonstrates the ethical problems that arise when screening programs are expanded in the absence of true understanding of the diseases involved. In its 5 years of testing and millions of dollars in costs, there have been very few benefits, and the testing has uncovered potential cases of late-onset disease that raise difficult ethical questions in their own right. For these reasons, we argue that Krabbe screening should only be continued as a research project that includes the informed consent of parents to the testing.

## Introduction

In 2006, New York State instituted the first newborn screening for Krabbe disease, though not at the behest of public health officials. The American College of Medical Genetics had just recommended a radical expansion of newborn screening programs in the USA but they explicitly refused to endorse screening for Krabbe (ACMG, 2006: 6S). Instead, the push for Krabbe screening was spearheaded by Hall-of-Fame quarterback Jim Kelly and his wife, Jill, whose son died from the disease, and who were able to convince Governor George Pataki to issue an executive order mandating the test. However, the New York State experience shows the problems with efforts to expand screening programs in the absence of true understanding of the diseases involved. In its 5 years of testing and millions of dollars in costs, there have been very few benefits, and the testing has uncovered potential cases of late-onset disease that raise difficult ethical questions in themselves. For these reasons, we argue that Krabbe screening should only be continued as a research project that includes the informed consent of parents to the testing.

## Background

Krabbe disease is an inherited, autosomal recessive, neurodegenerative disease caused by a deficiency in a lysosomal enzyme, galactocerebrosidase (GALC). At birth, children appear normal, but they soon develop irritability, spasticity, feeding difficulties, blindness and deafness. Soon their development slows and then stops. Eventually, the children cease to have any voluntary motion, and they die in childhood, often early (Duffner *et al.*, 2009a: 246). The disease is rare and occurs in about 1 in 100,000 births (Wenger, 2011). Until recently, there was no treatment, but hematopoietic stem cell transplantation (HSCT) using umbilical cord blood seems to result in significantly better outcomes for the recipients, but only if the transplant is done pre-symptomatically (Escolar *et al.*, 2005). The treatment is still experimental, and not all eligible patients have undergone the therapy. And it is far from benign: it involves chemotherapy to ablate the bone marrow of the patient, followed by HSCT, all on an infant less than 2 months old. HSCT carries an estimated 10 per cent risk of death and higher risk of morbidity (Duffner *et al.*, 2009a: 246). However, it seems to replace the missing enzyme, and the children that survive the procedure grow and develop, though in many cases, with significant disabilities; the exact long-term prospects are still unclear (Escolar *et al.*, 2005; Duffner *et al.*, 2009b).

Because HSCT is only effective if done pre-symptomatically, newborn screening is the only systematic way to find infants who could benefit from it. On that basis, advocates argued for its inclusion in the newborn screening panel. They claimed that it fit the model of other newborn screening programs, like that of

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phenylkentonuria (PKU), an inborn error of metabolism which causes severe cognitive disabilities unless the child is placed on a special diet before symptoms begin to appear in the first few months of life. Krabbe advocates believed that the screening and subsequent confirmatory enzyme assay would be sufficient to identify those infants with severe GALC deficiency, who would be appropriate candidates for HSCT.

Despite this comparison, testing for Krabbe disease does not meet the traditional criteria for medical screening, as outlined in the classic report by J.M.G. Wilson and G. Jungner (see Ross, 2012):

(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 stage.
(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 policy on whom to treat as patients.
(9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
(10) Case-finding should be a continuing process and not a 'once and for all' project (Wilson and Jungner, 1968: 26, 27).

If anything, we should expect a mandatory newborn screening program—which uses the power of the state to require all newborns to be tested—to meet all these criteria quite clearly.[1] But Krabbe testing does not do so. While the disease is serious, it affects a very small number of children, so New York State, with a birth rate of about 250,000 a year, expected to see only two cases a year, so it may meet criteria (1), but not clearly. The question then becomes whether the resources needed to detect these two cases might be better spent on other public health programs, and so Krabbe testing does not clearly meet criteria (9).

In addition, while the treatment is only effective if provided pre-symptomatically (4), that treatment is not well established (2). Indeed, in this respect, it is quite unlike PKU where the benefits of treatment for the child are so great that if parents are unable or refuse to provide the PKU diet, a strong case can be made for medical neglect. But parents who refuse the treatment for Krabbe are not clearly acting against the best interest of their child. These parents are faced with subjecting their 2-month-old infant to an unproven process that may itself damage, if not kill, their child with the end result that the child will be severely disabled. Against that option is the high probability—though, given our lack of knowledge about the disease, not the certainty—that their child will develop a disease that is certain to kill her in early childhood. We may disagree with a decision to forego treatment, but it is not so out-of-bounds that it would constitute medical neglect.

Finally, Krabbe testing fails to meet the Wilson–Jungner criteria because, although a test is available and relatively easy to administer (3), (6), what the results mean is still unknown (7), (8). Indeed, from the beginning, experts knew there might be complications in interpreting the results. While the infantile form of Krabbe disease is the focus of newborn screening, there are also late-onset forms. In these forms, symptoms may begin at any time, from the age of 6 months to late adulthood, and the patient's condition has a variable rate of deterioration that may not be related to the age of onset. HSCT has been tried for these forms, but it has not been consistently successful (Kolodny *et al.*, 1991; Krivit *et al.*, 1998; Duffner *et al.*, 2009a). So currently, there are no established treatments for the late-onset forms of Krabbe disease, and no clear benefit in pre-symptomatic testing of this cohort. Unfortunately, the newborn screening test and confirmatory GALC enzyme activity by themselves do not distinguish between the early infantile and late-onset forms. Furthermore, the natural history of late-onset Krabbe disease is so poorly understood that no one knows if or when a child at risk for the late-onset form of the disease will actually develop it. It thus burdens the parents and the child with knowledge that in no way benefits the child. It thereby adds stress to lives of these families and creates a cadre of 'patients in waiting', stuck indefinitely in a no man's land between illness and normality (Timmermans and Buchbinder, 2010).

To deal with the uncertainty that pervades the findings in the testing, the ad hoc group formed to implement the program in New York, the Krabbe Consortium (a group that includes one of us), devised a procedure to make recommendations to assess the risk of developing the infantile form of the disease based on GALC enzyme activity, on GALC genotype and on a comprehensive

medical evaluation of the infant[2] (Duffner *et al.*, 2009a: 248–50). Through this method, the Consortium has tried to pick out the infants who are most at risk for the infantile form of the disease and who might, therefore, benefit from HSCT. According to data collected and reviewed by the Consortium, in the first 5 years of testing, from August 2006 to August 2011, 1 million children have been screened for Krabbe disease. Of those, 228 had an initial positive test. Upon further testing, 114 of these were found to be normal. Of the remaining, 84 were considered 'low risk', meaning that their GALC enzyme activity was low, but apparently functional. The remaining 30 had low enzyme levels that were felt to put them at either moderate ($n = 19$) or high ($n = 11$) risk for the disease. None of those at moderate risk has shown any symptoms of Krabbe disease, but 13 of them have two GALC mutations. Whether these children in the moderate-risk category will develop a form of Krabbe disease later in life is unclear; certainly those with low GALC activity and two GALC mutations are at risk, both biochemically and genetically. Of the 11 infants found to be at high risk, all have two GALC mutations, and their particular mutations, enzyme activity, clinical evaluations and neurodiagnostic testing were reviewed to determine the likelihood that they would develop the infantile form of Krabbe disease. For seven of these 'high-risk' infants, the likelihood of onset in infancy was not thought high enough to recommend HSCT. None are known to have developed any symptoms of Krabbe disease at this time. The parents of the remaining four patients were encouraged to seek HSCT for their children. Of these four, the parents of one refused treatment and the child has developed Krabbe disease; the treatment of one was done after neurologic symptoms had developed, and the child has severe neurological problems; one had the treatment and is doing relatively well with motor delays; and one died of complications from the treatment.

In 5 years of Krabbe disease newborn screening and a cost of $3.5 million (Salveson, 2011: 98–102), the program has identified, at best, four cases for which the testing was designed. It has also created considerable frustration and anxiety for the families of some 20 other infants, who are told that their children *might* develop a devastating neurodegenerative illness, but that there is no good way to predict if, much less when, it would occur or how it might be avoided (DeLuca *et al.*, 2011; Salveson, 2011: 66–69, 75–82). For these families, the state has screened for a late-onset disease for which there is no pre-symptomatic treatment, subjected their children to a multitude of tests, created considerable anxiety and then told them that no one knows what the results mean and that there was nothing that could be done. Understandably, some parents became angry with the whole process (Salveson, 2011: 66, 67, 83–90).

## Confronting the future

The Krabbe program cannot, then, be considered a success. At best, it has effectively treated one infant, but in the process it has created considerable anxiety at a substantial cost to the state. We can respond to this situation in one of three ways.

First, we could abandon Krabbe newborn screening altogether, arguing that the benefits for the very few children who might be helped are outweighed by the cost of the program and the unwarranted anxiety it creates. Part of the argument would be that the Krabbe screening program was badly conceived in the first place as it mandates universal screening when the disease is so poorly understood. And part of the argument is that the money could be spent on other programs—like increased pre-natal screenings—that would save more lives (Baily and Murray, 2008). For just these reasons, the US Advisory Committee on Heritable Disorders in Newborns and Children has recently confirmed the conclusion of the ACMG report not to recommend Krabbe testing (Kemper *et al.*, 2010).

Second, we could continue to screen for Krabbe disease on the theory that we should treat the few cases we find and follow other at-risk children over time to understand better the natural history of the late-onset forms. Obviously, the case for this strategy would be stronger if the treatment for Krabbe disease were less risky and its benefits more clear. Nevertheless, we might still justify the testing by arguing that the best way—and perhaps the only way—to understand early and late-onset Krabbe disease would be to follow the patients at risk to discover which of them develops the disease and how it progresses when they do.[3] Such knowledge is crucial for our ability to develop treatments, and it can only be found by identifying pre-symptomatic patients with newborn screening. But if a key goal of the newborn screening program is to conduct research, then the State of New York appears to be forcing every newborn to participate in a research study without the consent of her parents. Even if no newborn is enrolled in one of the follow-up studies without the consent of her parents, the state has already coerced families into becoming *potential* research subjects, whether they want to be or not.

Finally, we could simply treat Krabbe testing as the long-term research project that it is. Under this plan, we would eliminate the *mandate* for Krabbe testing, so that we would no longer use the power of the state to force parents to test their children as the state does not have a compelling interest to do so. Instead, the test would be *recommended* to parents under a research protocol. In doing so, we would be able to achieve two goals: first, we could find and treat most cases of infantile Krabbe disease and thereby learn how to improve that treatment and second, we could gain important information about how late-onset forms develop in the hope that we can develop treatments for it in the future. As with any research program enrolling children, the state would need to obtain the consent of the parents after providing them with information about the disease, about the treatments for the infantile form and about the research program to follow all at-risk children. Then, at least, parents would know what to expect if their child tests positive, and they could decide if the program sounds too burdensome. This approach, in fact, seems to be favored by parents, who accept newborn screening for diseases that have no treatment because they want to prepare themselves, but who do not favor mandatory screening for late-onset diseases (Hasegawa *et al.*, 2011).

Nevertheless, this proposal has at least two problems. First, requiring consent implies that some parents will *not* consent to the testing, and that raises the possibility that a child with infantile Krabbe will be missed. Because the treatment is burdensome, parents can reasonably reject it, and if the parents would reject the treatment, then the screening is pointless. Gaining the consent of the parents, besides putting the research program on a better ethical footing, has an important side benefit: it would help to create an alliance between the researchers and parents by involving the parents in the process from the beginning, and it would thereby demonstrate respect for their role in their children's health. Such an alliance may prove crucial in helping parents make decisions if their children do develop Krabbe disease (Ross, 2010).[4] The limited experience of parental consent for newborn screening has shown that most parents will usually agree to testing if given the choice (Faden *et al.*, 1982; Botkin, 2009; Comeau and Levin, 2009), so we have reason to think that few, if any, children with disease will be missed.

The second problem is that requiring consent comes with a cost. Getting meaningful consent takes time and effort, and someone will have to pay for it. Past experience has had mixed results (Faden *et al.*, 1982; Laing and MacIntosh, 2004; Feuchtbaum *et al.*, 2007; Miller *et al.*, 2010; Ross, 2010: 304), so we cannot assume that the costs of the consent process will be negligible. In addition, as there will be some costs associated with setting up a mechanism by which only some of the newborn samples are tested for Krabbe, this proposal is likely to increase the costs of the program. These costs, of course, would be part of a research program, and we would have to decide if this research program is the best use of our limited research funds. So, even if this proposal is the best option for dealing with the ethical issues, it may still not win in a competition for research funding.

If such a research program is worthwhile, it should stand on its own merits, and it should not be conducted by hijacking the newborn screening mandate. By gaining the consent of the parents, the state can perform a valuable service by facilitating this research, but it should not coercively recruit patients into it. Thus, while requiring consent from the parents does not solve all of the ethical issues with Krabbe newborn screening, we think it presents the best available approach.

## Conclusions

As newborn screening continues to expand and ethical and social conflicts arise (Kemper *et al.*, 2010; Timmermans and Buchbinder, 2010; DeLuca *et al.*, 2011), now is the time to think about how to strike the balance between the ethical concerns. We think that states should proceed cautiously, but that they should be willing to be creative in managing potential conflicts. We make the following recommendations: (i) Mandatory newborn screening should be reserved for diseases that require pre-symptomatic treatment, but only if that treatment is well established and known to have good results and (ii) voluntary screening for diseases can be considered for other diseases, where we have some reason to believe that we can develop better therapies by learning more about the course of the disease. Voluntary screenings, of course, will always require the informed consent of the parents. Such a cautious approach may not be what some newborn screening advocates desire, but it is the best way to minimize the ethical harm that these programs can cause.

## Conflicts of interest

J.M.K. is a member of the Krabbe Consortium, an ad hoc group formed to help implement the Krabbe

Newborn Screening program in New York State. R.H.D. has no conflicts to report.

## Notes

1. The extent to which parents can opt out of newborn screening varies from state to state in the USA and from country to country, but even in those places where parents may opt out, they are often unaware that they may do so (Mandl *et al.*, 2002: 272; Kim *et al.*, 2003: e122; Clayton, 2005; Detmar *et al.*, 2007; DeLuca *et al.*, 2011: 58; Nicholls, 2012).
2. A nice flowchart of this process can be found in Kemper *et al.*, 2010: 541.
3. One such study has already been funded by National Institutes of Health to evaluate the progression of brain changes using advanced imaging techniques to develop better prognostic tools (Escolar, 2011).
4. For that reason, some ethicists think that *all* newborn screening should require parental consent (Ross, 2010).

## References

ACMG (American College of Medical Genetics). (2006). Newborn Screening: Toward a Uniform Screening Panel and System: Executive Summary. *Genetics in Medicine*, **8**, 1S–11S.

Baily, M. A. and Murray, T. H. (2008). Ethics, Evidence, and Cost in Newborn Screening. *Hastings Center Report*, **38**, 23–31.

Botkin, J. R. (2009). Research for Newborn Screening: Developing a National Framework. In Baily, M. A. and Murray, T. H. (eds), *Ethics and Newborn Genetic Screenings: New Technologies, New Challenges*. Baltimore: Johns Hopkins Press, pp. 212–236.

Clayton, E. W. (2005). Talking with Parents Before Newborn Screening. *Journal of Pediatrics*, **47**, S26–S29.

Comeau, A. M. and Levin, D. E. (2009). Population-based Research with a Public Health Service: Two Models for Compliance with the Common Rule in the Massachusetts Newborn Screening Program. In Baily, M. A. and Murray, T. H. (eds), *Ethics and Newborn Genetic Screenings: New Technologies, New Challenges*. Baltimore: Johns Hopkins Press, pp. 274–291.

DeLuca, J. M., Kearney, M. H., Norton, S. A. and Arnold, G. L. (2011). Parents' Experience of Expanded Newborn Screening Evaluations. *Pediatrics*, **128**, 53–61.

Detmar, S., Hosli, E., Dijkstra, N., Nijsingh, N., Rijnders, M. and Verweij, M. (2007). Information and Informed Consent for Neonatal Screenings: Opinions and Preferences of Parents. *Birth*, **34**, 238–244.

Duffner, P. K., Caggana, M., Orsini, J. J., Wenger, D. A., Patterson, M. C., Crosley, C. J., Kurtzberg, J., Arnold, G. L., Escolar, M. L., Adams, D. J., Andriola, M. R., Aron, A. M., Ciafaloni, E., Djukic, A., Erbe, R. W., Galvin-Parton, P., Helton, L. E., Kolodny, E. H., Kosofsky, B. E., Kronn, D. F., Kwon, J. M., Levy, P. A., Miller-Horn, J., Naidich, T. P., Pellegrino, J. E., Provenzale, J. M., Rothman, S. J. and Wasserstein, M. P. (2009a). Newborn Screening for Krabbe Disease: The New York State Model. *Pediatric Neurology*, **40**, 245–252.

Duffner, P. K., Caviness, V. S. Jr, Erbe, R. W., Patterson, M. C., Schultz, K. R., Wenger, D. A. and Whitley, C. (2009b). The Long-term Outcomes of Presymptomatic Infants Transplanted for Krabbe Disease: Report of the Workshop Held on July 11 and 12, 2008, Holiday Valley, New York. *Genetics in Medicine*, **11**, 450–454.

Escolar, M. L. (2011). *Diffusion Tensor Imaging (DTI) in Krabbe disease*. Study registered at Clinical Trials.gov., available from: http://clinicaltrials.gov/ct2/show/NCT00787865?term=krabbe+disease&rank=1 [accessed 6 September 2012].

Escolar, M. L., Poe, M. D., Provenzale, J. M., Richards, K. C., Allison, J., Wood, S., Wenger, D. A., Pietryga, D., Wall, D., Champagne, M., Morse, R., Krivit, W. and Kurtzberg, J. (2005). Transplantation of Umbilical-cord Blood in Babies with Infantile Krabbe Disease. *New England Journal of Medicine*, **352**, 2069–2081.

Faden, R., Chwalow, J., Holtzman, N. A. and Horn, S. D. (1982). A Survey to Evaluate Parental Consent as Public Policy for Neonatal Screening. *American Journal of Public Health*, **72**, 1347–1352.

Feuchtbaum, L., Cunningham, G. and Sciortino, S. (2007). Questioning the Need for Informed Consent: A Case Study of California's Experience with a Pilot Newborn Screening Research Project. *Journal of Empirical Research on Human Research Ethics*, **2**, 3–14.

Hasegawa, L. E., Fergus, K. A., Ojeda, N. and Au, S. M. (2011). Parental Attitudes Toward Ethical and Social Issues Surrounding the Expansion of Newborn Screening Using New Technologies. *Public Health Genomics*, **14**, 298–306.

Kemper, A. R., Knapp, A. A., Green, N. S., Comeau, A. M., Metterville, D. R. and Perrin, J. M. (2010). Weighing the Evidence for Newborn Screening for Early-infantile Krabbe Disease. *Genetics in Medicine*, **12**, 539–543.

Kim, S., Lloyd-Puryear, M. A. and Tonniges, T. F. (2003). Examination of the Communication Practices Between State Newborn Screening Programs and the Medical Home. *Pediatrics*, **111**, e120–e126.

Kolodny, E. H., Raghavan, S. and Krivit, W. (1991). Late-onset Krabbe Disease (Globoid Cell Leukodystrophy): Clinical and Biochemical Features of 15 Cases. *Developmental Neuroscience*, **13**, 232–239.

Krivit, W., Shapiro, E. G., Peters, C., Wagner, J. E., Cornu, G., Kurtzberg, J., Wenger, D. A., Kolodny, E. H., Vanier, M. T., Loes, D. J., Dusenbery, K. and Lockman, L. A. (1998). Hematopoietic Stem-cell Transplantation in Globoid-cell Leukodystrophy. *New England Journal of Medicine*, **338**, 1119–1126.

Laing, I. A. and MacIntosh, N. (2004). Practicalities of Consent. *Lancet*, **364**, 659.

Mandl, K. D., Feit, S., Larson, C. and Kohane, I. S. (2002). Newborn Screening Program Practices in the United States: Notification, Research, and Consent. *Pediatrics*, **109**, 269–273.

Miller, F. A., Hayeems, R. Z., Carroll, J. C., Wilson, B., Little, J., Allanson, J., Bytautas, J. P., Paynter, M., Christensen, R. and Chaktraborty, P. (2010). Consent for Newborn Screening: The Attitudes of Health Care Providers. *Public Health Genomics*, **13**, 181–190.

Nicholls, S. G. (2012). Proceduralisation, Choice and Parental Reflections on Decisions to Accept Newborn Bloodspot Screening. *Journal of Medical Ethics*, **38**, 299–303.

Ross, L. F. (2010). Mandatory Versus Voluntary Consent for Newborn Screening? *Kennedy Institute of Ethics Journal*, **20**, 299–328.

Ross, L. F. (2012). Newborn Screening for Lysosomal Storage Diseases: An Ethical and Policy Analysis. *Journal of Inherited Metabolic Disease*, **35**, 627–634.

Salveson, R. (2011). *Expansion of the New York State Newborn Screening Panel and Krabbe Disease: A Systematic Program Evaluation.* New York: Dissertation, Columbia University.

Timmermans, S. and Buchbinder, M. (2010). Patients-in-waiting: Living Between Sickness and Health in the Genomics Era. *Journal of Health and Social Behavior*, **51**, 408–423.

Wenger, D. A. (2011). Krabbe Disease. In Pagon, R. A., Bird, T. D., Dolan, C. R., Stephens, K. and Adam, M. P. (eds), *GeneReviews*. Seattle: University of Washington.

Wilson, J. M. G. and Jungner, G. (1968). *Principles and Practice of Screening for Disease*. Public Health Papers 34, Geneva: World Health Organization.

# Newborn Screening for Krabbe Disease: What Illinois Can Learn from New York

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Dees and Kwon review the lessons learned since 2006 when New York State (NYS) adopted newborn screening for Krabbe disease as part of their mandatory newborn screening (NBS) panel and conclude that 'Krabbe screening should only be continued as a research project that includes the informed consent of parents to the testing' (Dees and Kwon, 2013).

Dees and Kwon are not the first to propose that newborn screening expansions be developed as research protocols (Botkin, 2005; Natowicz, 2005; Ross and Waggoner, 2012). Nevertheless, their review of the NYS Krabbe pilot comes at a critical time as Illinois is about to embark on NBS for Krabbe disease and six other lysosomal storage disorders (LSDs), 'when the conditions set out in the statute have been met (Hasbrouck, 2012: 1). The conditions include the establishment and verification of relevant and appropriate performance specifications; the availability of quality

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