Parents: Critical Stakeholders in Expanding Newborn Screening

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Lysosomal storage diseases (LSD) are rare genetic conditions that can affect individuals at different stages of life. Hunter Kelly (February 14, 1997 to August 5, 2005), the son of former Buffalo Bills quarterback Jim Kelly, died of complications from infantile Krabbe disease, one of the LSDs.[1] Bone marrow transplantation can sometimes slow down the progressive neurologic symptoms caused by Krabbe disease.[2] Mr Kelly advocated that the New York State Public Health Department screen for Krabbe disease to diagnose it early enough that bone marrow transplantation is an option. In August 2006, New York implemented Krabbe screening into its mandatory screening program.

In Illinois, in 2005, Bob and Sonya Evanosky successfully lobbied the Illinois legislature to mandate screening for 5 LSDs to be incorporated into its mandatory newborn screening program, including Krabbe disease, Pompe disease, and Fabry disease. This screening was to begin within 6 months after the establishment and verification of relevant and appropriate performance specifications; the availability of quality assurance testing methodology for these processes; and the establishment of precise threshold values ensuring defined disorder identification for each screening test.[3] Since then, the Evanosky Foundation has convinced the Illinois legislature to add 2 additional LSDs to the mandatory newborn screening program. Through their advocacy organization, they have also lobbied for LSD screening in Missouri and New Mexico.[4] The reports from New York should make us think twice about the clinical value of LSD screening[5] and question the political approach to expand screening that circumvents a more evidence-based public health approach.

New York was not the first jurisdiction to perform newborn screening for LSD. Both Taiwan and Italy have had research protocols to study the feasibility and utility of screening for Pompe disease (Taiwan)[6] and Fabry disease (Taiwan[7] and Italy[8]). In all cases, the implementation was performed with parental consent, and the protocols underwent review by a human subjects protection committee (known as an institutional review board [IRB]). In contrast, New York implemented screening into mandatory screening, which does not require parental consent, let alone parental notification. No IRB was involved.

We learned a lot from the New York experience. Data from the Hunter's Hope Registry suggested that 90% of cases identified would be of infantile-onset form.[9] In the first 4 years of newborn screening in New York, 300 children were called back for confirmatory studies.[10] Twenty-nine tested positive. Four (14%) were found to have the infantile form of the disease, and to date, one died without a transplantation, one died during the transplantation, one underwent transplantation but is doing poorly, and one is doing well. Another 25 children were classified as being at moderate-to-high risk of developing a form of Krabbe disease, but none have developed any symptoms, although they have become "patients in waiting."[11] Some may develop symptoms later in childhood, others in adulthood, and neither genetic testing nor biochemical assay can reliably predict when or if symptoms will develop. New York has elected not to follow the children identified by screening as moderate-to-high risk because of the psychological and emotional stress that the diagnosis and close monitoring may cause.[10]

What we have learned from New York's Krabbe screening program, then, is how incompletely we understand the natural history of Krabbe disease and that late-onset Krabbe is likely to be more common than clinically diagnosed. Both are reasonable outcomes of a research study in which one voluntary enrolls one's child but not reasonable outcomes of a universal mandatory screening program in which most experts in public health screening support the Wilson and Jungner criteria[12] (albeit with some modifications[13,14]). The Wilson and Jungner criteria include an adequate understanding of the natural history of the condition, a recognizable latent or early symptomatic stage, and an agreed policy regarding whom to treat as patients.[12-14] Understood as a research project, different rules would apply to newborn screening for Krabbe disease. The first principle of research, as enumerated in the Nuremberg Code, is the requirement to get consent of the participants[15] (or of their surrogates, if the participant is too young to provide consent).[16] It is immoral to perform research on living persons without consent,[15,16] and it also violates the Federal Regulations for Human Subjects Protections,[17] although to date, no one has legally challenged the program.

We learned a lot from the other pilot screening programs for lysosomal screening diseases. From Italy, we learned that most cases of Fabry disease are adult-onset. Spada et al[8]

ACMG	American College of Medical Genetics
HRSA	Health Resources and Services Administration
IRB	Institutional review board
LSD	Lysosomal storage diseases
SACHDNC	Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

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reported on their research findings, and Italy no longer screens for the condition. Researchers from Taiwan also evaluated Fabry disease and concluded that it did not yet meet the criteria for population newborn screening,[7] although newborn screening for Fabry disease is offered under a research protocol that continues to require parental consent (W.-L. Hwu and Y.-H. Chien, personal communication, October 2011). From Taiwan, we also learned that most cases of Pompe disease are adult-onset and that the screening tests had a high false-positive rate (labeling children who were not at risk).[6] Taiwan has reduced this problem and has elected to incorporate Pompe disease screening into their standard panel yet continue to seek parental consent (W.-L. Hwu and Y.-H. Chien, personal communication, October 2011).

The Uniform Panel

In 2005, the American College of Medical Genetics (ACMG), in collaboration with the Health Resources and Services Administration (HRSA), developed a Uniform Panel of conditions that were recommended for newborn screening.[18] In the report, investigators evaluated 83 conditions and determined that 29 should be included as primary targets for newborn screening and 25 additional conditions as secondary targets.[18] At the federal level, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) adopted the recommendations despite criticisms that: (1) some of the conditions failed to meet public health screening criteria defined by Wilson and Jungner; and (2) that the ACMG/HRSA committee used criteria that placed too much emphasis on platform technologies and not enough on direct benefit to the child.[19,20] When the LSDs were evaluated using the ACMG/HRSA criteria in 2005, no LSD met the criteria for inclusion in this panel. Most recently, advocates of patients with Krabbe disease asked SACHDNC to re-evaluate Krabbe disease for inclusion in the uniform panel. SACHDNC assigned it to their external Evidence Review Workgroup,[21] and Krabbe disease was again rejected.[22]

Despite the federal decision, several states are developing protocols to screen for LSD and will, like New York State, incorporate them into routine newborn screening, which does not require parental consent. The mandatory nature of newborn screening is anachronistic in that it is the only testing of children that is performed without parental permission and was made mandatory despite national recommendations that argued in favor of parental permission[23]— recommendations that have been reaffirmed over the decades.[24-26] The major force behind making newborn screening mandatory was Dr Robert Guthrie, who developed the filter paper-based bacterial inhibition assay for phenylketonuria, with major support from the National Association of Retarded Children (NARC, now referred to as The ARC). Guthrie and The ARC members lobbied state governments and provided draft legislation.[23] Today, screening is mandatory in 48 states, although, with the exception of Nebraska, all states allow parents to opt out, although they differ in what reasons parents may give for refusing.[26] In Illinois, screening is mandatory, but parents can refuse on religious grounds.

A problem with incorporating LSD screening into the state-screening programs is that newborn screening is an "all-or-nothing" refusal. Parents cannot say that they want their child to be tested for some conditions and not others. Because some of the conditions that we screen for can have symptoms in infancy and may require prompt treatment to prevent death or disability (eg, phenylketonuria, sickle cell disease, hypothyroidism), the harm of a missed or delayed diagnosis can be severe, and there is broad pediatric health professional consensus to discourage parental refusals.

Expanding Newborn Screening in Illinois

In 1997, Hiller et al[27] reported that 36 states have advisory committees, 26 of which included public members. They also reported that "[t]hirty-three states report that members of the public have had a role in consideration of additions to the newborn screening battery" (p. 1284).[27] However, there are no guidelines as to the appropriate membership and whether there should be differential weighting of voting on these committees taking into account experience with medical care delivery and public policy.

In Illinois, the Department of Public Health has a Genetic and Metabolic Advisory Committee with broad membership from the medical community as well as community members. All members have an equal vote. There is a process to evaluate the appropriateness of adding conditions to the newborn screening panel. Despite this structure and process, advocacy groups have sidestepped this Committee in Illinois by successfully lobbying for legislation.[4] However, the legislation that the Evanosky Foundation supported was poorly conceived because it required the state to test for conditions for which screening tests did not yet exist. By going to the legislature, the Foundation also failed to engage those who would be responsible for its implementation (eg, the Department of Public Health and the pediatric providers who care for newborns), who could have provided guidance about the suitability of screening for particular conditions given current testing abilities and treatments.

A problem with parent advocacy groups directing the expansion of newborn screening is that their arguments are founded on anecdotal experience rather than scientific peer-reviewed evidence.[28] The historian Diane Paul has shown that early parent advocacy groups were imbued with a public health ethic, but now writes that "This ethic has apparently eroded over time as the result of both broad social changes and the increasing entanglement of such groups with pharmaceutical and biotechnology companies."[29] Rothman et al[30] concur: "Organizations that once served the public interest have become devoted to their members' interests." This may be attributable in part to the source of funding. Although private individuals and charitable foundations were the historical source of funding for advocacy groups, today advocacy groups are often funded by pharmaceutical