

CONTRIBUTORS: Jeffrey P. Brosco, MD, PhD,^a Lee M. Sanders, MD, MPH,^a Robin Dharia, BS,^a Ghislaine Guez, BS,^a and Chris Feudtner, MD, PhD, MPH^b

^a*Department of Pediatrics, University of Miami, Miller School of Medicine, Miami, Florida; and* ^b*Division of General Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*

Address correspondence to Jeffrey P. Brosco, MD, PhD, PO Box 016820 (D-820), Miami, FL 33101. E-mail: jbrosco@miami.edu

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ABBREVIATION

NBS—newborn screening

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The Lure of Treatment: Expanded Newborn Screening and the Curious Case of Histidinemia

In the last decade, universal newborn screening (NBS) has entered a new era of promise and controversy. With the use of tandem mass spectroscopy, states have substantially increased the number of conditions included in mandatory NBS programs.¹ This expansion has mostly followed recommendations from an expert panel commissioned by the Maternal and Child Health Bureau, which proposed mandated screening for a core panel of 29 conditions and suggested that 25 additional conditions be reported to families, although accepted treatments are not yet available.² The President's Council on Bioethics³ criticized the recommendations, arguing that mandated NBS should be restricted to conditions that adhere closely to Wilson and Jungner's traditional principles for screening,⁴ especially the availability of treatment that is accepted as effective and accessible to patients. Others have countered that exclusive focus on treatment of the infant ignores other potential benefit to families and society and that the time has come to supplant treatment availability as the key criterion for NBS programs.^{5,6}

These policy debates may seem to arise from access to new technology, but in fact similar issues arose in the early history of NBS. For example, NBS for phenylketonuria is justly celebrated as a public health success, but in the mid-1960s clinicians and policy makers faced profound ethical issues. NBS revealed many children with intermediate serum val-

ues of phenylalanine, and because clinicians did not know the natural history of these metabolic variants, they could not accurately weigh the risks and benefits of a restricted diet. A prospective, placebo-controlled study was never conducted, because withholding an accepted treatment, even if it had uncertain value, was deemed unethical.⁷

The curious case of NBS for histidinemia highlights another potential pitfall of justifying NBS on the basis of the availability of treatment. A disorder of amino acid metabolism that initially seemed to be similar to phenylketonuria, histidinemia was first identified as a potential cause of intellectual disability in the early 1960s, and reports of dietary restriction normalizing patients' biochemical profiles soon followed. Many early published reports, however, noted typical cognitive development without treatment, and by 1974 Levy et al⁸ argued that histidinemia was likely to be a normal metabolic variant. By the early 1980s, apparent consensus emerged that treatment and screening were unnecessary, and no author ever unequivocally recommended NBS (Fig 1). Nonetheless, from the early 1970s through the 1990s, at least 3.5 million children were screened for histidinemia as part of state NBS programs in Massachusetts and New York, and dozens of children were treated with low-histidine diets. Although there have been no reports of physical harm to any of these children, they and their families endured the

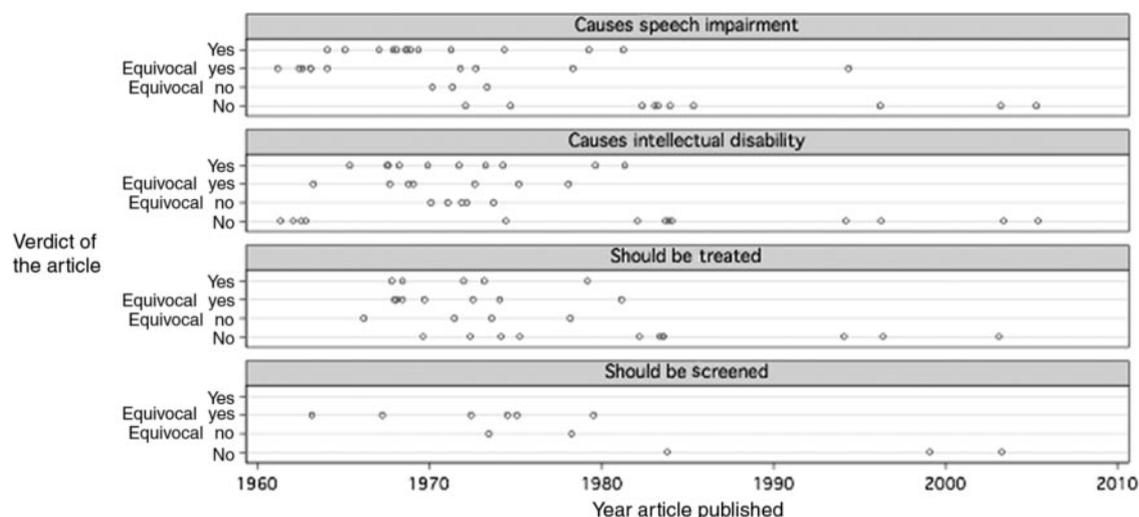


FIGURE 1

All English-language publications regarding histidinemia are depicted based on the original authors' conclusions regarding whether histidinemia caused impairment, required treatment, or should be added to state NBS programs.⁹

burdens of a restricted diet, repeated blood draws, and uncertainty about the future. There were financial and opportunity costs to the families and society and reports of psychological stress for families of children with false-positive results.⁹

As noted by Levy¹⁰ and others,¹¹ the history of NBS for histidinemia is a cautionary tale. NBS programs for histidinemia began before there was clear evidence of harm and, in retrospect, can be cited as a reason to be wary of the rapid expansion of NBS programs.^{12,13} The decision to start NBS for histidinemia is most revealingly understood, however, in historical context. In the early 1960s the Kennedy family had begun drawing attention to people with intellectual disability, and many scientists and advocates believed that the systematic application of scientific medicine would eliminate most causes of intellectual disability by the end of the century.¹⁴ Early detection and treatment of phenylketonuria was the first of many successes, according to this perspective, and federal resources poured into research and training in developmental disabilities. At the national level, identification and treatment of histidinemia seemed to be one of many metabolic pieces that would fit together to solve the puzzle of intellectual disability.

Among state governments, which have always controlled NBS programs throughout the United States, adding histidinemia to the screening routine seemed to make sense in the early 1970s. Confronted by the high cost of maintaining residential institutions for people with developmental disabilities, state legislators could view NBS and early treatment of conditions such as histidinemia as an appropriate investment of resources that would improve health and re-

duce costs in the long run. As some recent commentators have argued, state legislators may have been readily influenced by a small number of passionate advocates, especially when pitted against abstract notions of opportunity cost and public health priorities.¹⁵ Indeed, a 1978 review of the New York State NBS program concluded that adding conditions such as histidinemia to the screening routine was partly based on the “rational need to identify and treat certain conditions at the earliest possible time, partly on the ease with which certain other tests could be added (regardless of their need to be diagnosed at birth), and partly on political expediency.”¹⁶

Two lessons can be gleaned from the history of NBS for histidinemia. First, our thinking about specific aspects of NBS programs may well be influenced, and potentially biased, by larger forces that become clearer only through the longer lens of history. For example, NBS programs fit neatly into the overall mindset of US medicine since the mid-20th century, wherein the key to improving health has been through the application of technologic advances that prevent or treat illness.¹⁷ Although this approach has certainly led to reduced morbidity and mortality, success has often been less than predicted,¹⁸ as highly touted novel therapies have subsequently been found to have little value or even pose harm.¹⁹ Decisions about NBS programs are likely still influenced by this mindset, whereby our efforts to understand the genetic causes of disease may lead us, almost reflexively, to overestimate the value of expanding NBS programs.

Second, this brief history of NBS for histidinemia confirms the importance of an adequate understanding of the natural

history of a condition. The natural history of rare conditions and their inevitable metabolic and clinical variants, can usually only be understood by screening large populations through NBS. This implies that state NBS programs may have a legitimate research component as part of their public health warrant. Botkin²⁰ and others^{21,22} have suggested a model of using retrospective controls from NBS programs when testing new treatments, but many state NBS programs have resisted using samples for research. The history of histidinemia suggests that studying the natural history of a condition, and avoiding lunging too hastily at the lure of a newly available treatment, may be a sufficient reason to perform NBS for selected conditions. Innovative models of informed consent will be necessary for such research.

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