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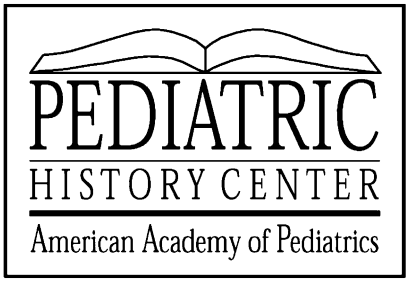
Pediatrics 2013;132;987; originally published online November 25, 2013;
DOI: 10.1542/peds.2013-1441



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Accepted for publication Sep 24, 2013

KEY WORDS
history, phenylketonuria, newborn screening, genetics

ABBREVIATIONS
NBS—newborn screening
PKU—phenylketonuria

doi:10.1542/peds.2013-1441

The Political History of PKU: Reflections on 50 Years of Newborn Screening

Just over 50 years ago, Dr Robert Guthrie developed a simple screening test for phenylketonuria (PKU) that became the prototype for universal newborn screening programs. Historians Jeffrey Brosco and Diane Paul explore why PKU screening marked a historical turning point in public health. It is a story that has left a far more complex legacy than most pediatricians recognize.

—Jeffrey P. Baker

Section Editor, Historical Perspectives

Phenylketonuria, or PKU as it is more familiarly known, is a rare disorder, affecting only ∼1 in 15 000 people. In the United States, for example, ∼275 infants will be born with the disease each year.[1] Thus in a lifetime of practice most pediatricians will not encounter a single case. Yet probably every pediatrician in the industrialized world has learned about PKU during medical school, many parents vividly remember the heel-stick test for their newborn, and scientists interested in genetics and metabolism say that they hope to "find another PKU." Why has such a rare condition garnered so much attention?

PKU is famous in part because it is widely seen as a victory for scientific medicine. If the condition is detected in the newborn period and a specialized diet is instituted, the profound cognitive impairment usually caused by PKU is averted. For the diet to be effective, however, the otherwise normal-appearing infant with PKU must be identified, among thousands of other nonaffected infants, in the first weeks of life. In the early 1960s, parents of children with intellectual disability began to advocate for state laws to test all newborns in the United States, and the first state laws for universal newborn screening (NBS) were implemented 50 years ago. By 1965, 32 American states had enacted screening laws, all but 5 making the test compulsory. By the mid-1970s, NBS for PKU had become routine in nearly every industrialized nation, and had even extended to many poorer countries.[2]

At first this may not seem different from many other 20th century success stories of scientific medicine: advances in the treatment and control of polio, smallpox, and typhoid fever (to name a few) required novel public health techniques based on advances in laboratory and clinical medicine. These "victories" for modern medicine were over relatively common conditions, however, and did not require that the state become involved in the daily practice of medicine in an on-going way. PKU is a rare condition, and appropriate treatment requires testing millions of unaffected infants, under state sponsorship, an anomaly in health care systems like that of the United States, where government typically has a limited role in individual medical care. How did a disease of marginal public health significance become the object of an unprecedented system for the routine testing of newborns, and how did it acquire paradigmatic status in the domains of public health and genetics?

The answer is that PKU is like an elusive protagonist, a potent cultural symbol that could be deployed to confront emerging issues in science and medicine.[2] Starting in the 1960s, scientists, politicians, and the general public were excited by the seemingly miraculous outcomes of diet-treated PKU infants: they viewed this success as an example of the enormous potential of science to transform the lives of people with intellectual disability, a cause célèbre in the mid-20th century. It seemed that many more examples were sure to follow, with the ability to intervene clinically in PKU portending effective treatments for other cognitive

disabilities. Even today clinicians perform extensive diagnostic testing on people with cognitive disabilities in hopes of finding a simple medical cure, despite the relatively small impact of PKU and similar conditions on the prevalence of intellectual disability in the late 20th century.[3]

In the 1970s and 1980s, PKU took on new roles as an exemplar in the nature-nurture debates and as a resource for advocates of genetic testing.[2] PKU is a genetic condition that is highly treatable if infants receive a diagnosis at birth and are placed on a diet low in phenylalanine, an essential amino acid found in all dietary proteins. That an environmental intervention could dramatically alter the course of a genetic disorder made it an attractive example both for critics of genetic determinism, who employed it in both the genetics of IQ and sociobiology controversies, and for enthusiasts for genetic screening, who traded on the "large store of goodwill and ethical credit" accumulated by NBS to legitimate genetic screening programs more generally.[4] Foes of genetic determinism and promoters of genetic tests have not generally been political bedfellows, and indeed, are often at odds; yet both find support for their positions in the history of PKU.

In the 1990s and 2000s, PKU served as the paradigmatic example for advocates eager to expand NBS. Twenty-first century NBS programs can potentially identify dozens of conditions, and proponents of expansion continue to use PKU to underscore the value of screening infants for disease. However, advocates inherit not just the goodwill generated by the success of treatment of PKU, but also the challenges arising from the fact that NBS programs were established a half-century ago in specific historical conditions that do not necessarily obtain today. For example, NBS programs are almost everywhere de facto or *de jure* mandatory, with no provisions for informed consent. Many professionals and parent organizations would now like to test for conditions that are much less treatable than PKU or that may provide no direct medical benefit at all to the child. Moreover, the dried blood spots collected from millions of newborns, representing an unselected population, have become a valuable resource for researchers. But these potential clinical and research practices, which would seem to require specific informed consent from parents, are not easy to harmonize with a legal framework and hospital routines that date from the 1960s.[2]

The regularity with which PKU was and is invoked in the service of divergent agendas is intriguing and prompts an obvious question: How well does this ubiquitous PKU success story accord with reality? Accounts of PKU diagnosis and treatment in the nonspecialist literature rarely mention any diagnostic complications, treatment challenges, or imperfect outcomes. The authors of a recent *Nature* article, for example, assert that treatment of newborns with PKU and other metabolic and immunologic disorders "is often as simple as diet change." [5] A common analogy has been to insulin, as in a 1964 *New York Times* report on the new law mandating PKU testing: "The disability can be detected by a simple blood test and can be corrected by a special diet in much the same way as diabetics are enabled to lead normal lives by the use of insulin."[6] It turns out that PKU is indeed like type 1 diabetes, though not as the *Times* writer intended. As anyone with either a personal or professional interest in diabetes (or PKU) knows, therapy for these conditions involves a lifelong struggle with personal behaviors and medical management. The diet allows extremely limited choices (Table 1) and interferes with the social and cultural aspects of eating. In this way one strand of the history of PKU follows the contours of the discovery of insulin: the famous breakthrough of scientific medicine does indeed save lives and reduce morbidity, but only through the arduous and uncertain path of living with a chronic condition.[7]

TABLE 1 Typical Low-Phenylalanine Diet for a 5-year-old Boy

Meal	Phenylalanine, mg
Breakfast	
Kid cereal, 6 tbsp	30
Banana, 6-in section	30
Orange juice, 4 oz	15
Phenyl-free formula, 6 oz	0
Lunch	
Vegetarian vegetable soup, 1/2 can	60
Saltine crackers, 2	30
Lettuce, shredded, 1/2 cup	15
French dressing, 2 tbsp	Free
Fruit cocktail, 3/4 cup	15
Phenyl-free formula, 6 oz	0
Snacks	
Popsicle	Free
Sucker, 1	Free
Apple, 1 medium	8
Phenyl-free formula, 6 oz	0
Dinner	
Rice, cooked, 4 tbsp	60
Green beans, cooked, 3 tbsp	15
Jelly gelatin, 6 tbsp	30
Phenyl-free formula, 6 oz	0
Kool-Aid, 4 oz	Free
Total	278

From Kaufman M, Nardella M. A teacher's guide to PKU. Texas Department of Health. 1985. Available at: www.pkuil.org/TeachersGuide.pdf. Accessed October 2, 2013

In the end, PKU will always be remembered as the first condition for which newborns were screened. This dramatic success is rightfully celebrated as a major victory for modern medicine. But the continuing value of PKU in policy debates is explained by the paucity of more powerful examples of the success of modern scientific medicine in preventing intellectual disability, altering the course of genetic disease, or dramatically changing outcomes through NBS. Despite great promise over the last 50 years, there have been precious few victories in these realms comparable to

the success of testing and treatment of PKU. That is why it continues even today to serve as an exemplar for diverse constituencies.

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This essay was adapted from The PKU Paradox: A Short History of a Genetic Disease by Diane B. Paul and Jeffrey P. Brosco. Published by The Johns Hopkins University Press, 2013. Reprinted by permission of the publisher.

JPB obtained funding, made substantial contributions to study design and interpretation of results, and collaborated in drafting the manuscript. DBP obtained funding, created study design, carried out archival research and structured oral interviews, made substantial contributions to interpretation of results, and collaborated in drafting the manuscript.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Brosco received support from the HRSA/MCHB Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (subcontract number 06-C210-01) and an Arsht Distinguished Ethics Faculty Award at the University of Miami (2012-14). Dr Paul received support from the National Institutes of Health, grant 1R03HG003730-01 (2005-2007). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.