Promoting Safe and Effective Genetic Testing in the United States

Final Report of the Task Force on Genetic Testing

EDITED BY

Neil A. Holtzman, M.D., M.P.H.

AND

Michael S. Watson, Ph.D.

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APPENDIX 5. THE HISTORY OF NEWBORN PHENYLKETONURIA SCREENING IN THE U.S.[a]

Diane B. Paul[b]

INTRODUCTION

Phenylketonuria (PKU) is a rare genetic disorder, with an incidence in the U.S., Britain, and most of Western Europe of between 1 in 11,000 and 1 in 15,000 births.[1] Virtually all newborns are tested for it in every American state, Canada, Australia, New Zealand, Japan, the nations of Western and most of Eastern Europe, and many other countries throughout the world. Normally, such a rare condition would not attract such attention, but PKU is a treatable genetic disease.

In the past, it generally resulted in severe mental retardation and behavioral and other abnormalities. About 90 percent of those affected had IQs of less than 50.[2,3,4] The symptoms of the disease result from a deficiency in a liver enzyme that catalyzes the conversion of phenylalanine (an essential amino acid that cannot be synthesized by humans) to tyrosine. In the absence of therapy, phenylalanine accumulates to toxic levels in the blood. Fortunately, mental retardation can be prevented and other symptoms mitigated if newborns are placed on a special diet from which most of the phenylalanine has been removed.

Thus, PKU screening provides an attractive example to proponents of genetic medicine and has come to be considered the "epitome of the application of human biochemical genetics," and a model for genetic medicine and public health.[5] Its appeal is partly explained by the dearth of other examples of effective interventions for genetic disorders. In general, advances in genetic knowledge have not been matched by corresponding progress in treatment (resulting in a "therapeutic gap").

At the same time, it demonstrates that "genetic" should not be equated with "unchangeable." PKU is an inborn error of metabolism, and it is our knowledge of its biochemistry that enables us to limit the supply of the damaging substrate and avoid or mitigate the symptoms of the disease. Thus, PKU also is frequently applauded by critics of genetic determinism, even when they are otherwise skeptical of the value of screening programs.[6,7]

Since PKU has acquired symbolic meaning to groups with disparate and even conflicting perspectives on policy issues in genetics, it is perhaps not surprising that accounts of screening and treatment have often been idealized. But the reality is quite complex.

Broad-based PKU screening began in 1963, when, following the invention of a vastly improved test to detect PKU in infants, Massachusetts became the first state to mandate screening—that is, to make screening of all newborns compulsory by law. The National Association for Retarded Children (NARC), an organization representing parents of retarded children and professionals in the field, advocated the screening and found that its application was very uneven. For example, in 1964, in Massachusetts maternity hospitals, virtually all infants were screened, but in thirty-two other states, fewer than half of the hospitals had instituted screening programs. The NARC proposed a model law, and, with officials of the Children's Bureau of the Department of Health, Education, and Welfare and of state departments of public health,[8] promoted mandatory screening.

[a]The Task Force commissioned this paper and reviewed an early draft of it. The views expressed in this paper are those of the author and do not necessarily reflect the views of the Task Force.

[b]University of Massachusetts at Boston

Health, Education, and Welfare and of state departments of public health,[8] promoted mandatory screening.

By 1975, forty-three states had enacted such laws and 90 percent of all newborns were being tested.[9] Today, every American state screens newborns for PKU and congenital hypothyroidism. Nearly all screen for additional metabolic disorders as well.[10] In only two states (Maryland and Wyoming) is explicit parental consent required for every screening program.[11]

Mandated screening was opposed by the American Medical Association and many state medical societies. More surprisingly, compulsory screening was also opposed rather quietly by many researchers in the field of human metabolism. For a variety of reasons, these researchers believed it premature to mandate that every infant be tested for PKU and their reservations intensified during the first few years of the screening programs.[12,13,14,15,16,17]

By almost any standard, though, PKU screening counts as a success. At relatively low cost, it has prevented mental retardation in thousands of infants worldwide. It is a significant achievement that these individuals and their families have been spared the devastating effects of the disease. But treatment has not been easy to manage, has not been completely efficacious, and has greatly exacerbated the problem of "maternal PKU."

It is of special interest that many of the problems accompanying screening and treatment were in fact anticipated by human metabolic researchers.

PKU SCREENING: THE EARLY YEARS

As early as the 1930s, biochemists George Jervis and Richard Block in the U.S. and Lionel Penrose in Britain proposed treating affected infants with a low-phenylalanine diet.[18,19,20] But for a number of reasons (including assumptions about the cost of producing the synthetic food), these early proposals were not pursued.

The idea that a phenylalanine-restricted diet could prevent or diminish symptoms associated with PKU was revived in 1951 by English biochemists Louis Woolf and David Vulliamy.[21] Woolf and colleagues tested the theory on three small children, all of whom showed some improvement.[22] Other researchers in Britain and the U.S. reported improvement in small numbers of older infants and children treated with a low-phenylalanine diet.[23,24,25,26,27] Although the first retrospective statistical study assessing the benefits of dietary therapy would not appear until 1960,[28] these reports generated great excitement for they held out hope that mental retardation, then considered therapeutically hopeless, might in fact be treatable.[29]

Notwithstanding some early claims that dietary therapy markedly increased the IQs of severely retarded children so that they might even be able to attend school, it was becoming increasingly clear that once retardation occurred, it could not be reversed.[30,31] Reviewing the experience between 1950 and 1959 with dietary therapy, Horst Bickel and Werner Grueter noted that the chances of cognitive improvement were greatest in the youngest patients and concluded: "Every effort should be made to start the diet in early infancy, if possible, within the first few months of life."[32] Identification of the infants with PKU would require population-wide screening (unless testing were restricted to the newborn siblings of previously affected children, a pool containing only a small proportion of all cases).[33] These considerations, and the availability of Lofenalac, a commercially-available formula approved by the FDA in 1958 (based on experience with just six

patients) prompted some hospitals, clinics, and private physicians to begin testing newborns for the disease.

However, the ferric chloride urine test, then the only method available, was unreliable until the age of six to eight weeks, after the infant had been discharged from the hospital and possibly after he or she had already suffered some irreversible brain damage. It was thus unsuitable for mass screening.

In 1960, the microbiologist Robert Guthrie (who had a mentally retarded son and niece, the latter diagnosed with PKU) developed an inexpensive, sensitive, and simple bacterial inhibition assay that could be administered a few days after birth. At the urging of the President and the Executive Director of the NARC, he published his report on the test quickly, as a letter to the editor, so that it could be publicized in connection with the NARC's 1961 poster featuring two little sisters with PKU.[34] This mode of announcement, and the fact that a peer-reviewed report on the test was not published until 1963 [35] led to some tensions with the community of human metabolic researchers. The situation was exacerbated when Guthrie—an outsider to the community—took his case directly to parents, legislators, and the press.

In late 1961, the Children's Bureau began a field trial involving over 400,000 infants in 29 states to assess the assay's suitability for a national screening program. By the time the trial ended in 1963, the Bureau had adopted the slogan, "Test Every Newborn For PKU."

Development of the Guthrie test converged with new thinking about the intractable problem of mental retardation. During the 1950s, public and private agencies had begun to reconsider their traditional emphasis on educational, social, and rehabilitative services for the retarded. A turn toward scientific prevention appeared increasingly attractive to government agencies, legislators, and the NARC.[36] The hope was that "the same scientific methods which have accomplished so much in the conquest of other diseases can now be harnessed to the study of mental defects."[37]

Even before development of the Guthrie test, this shift in emphasis was accompanied by strong claims for the significance of screening programs. In spite of its rarity, the prevention of PKU was portrayed as a means to substantially reduce the frequency of retardation. For example, the *New York Times* (April 7, 1957) explained the emphasis on early detection of retardation in a new government program for the preschool mentally retarded on the grounds that "much" mental retardation results from the treatable hereditary diseases, PKU and (the even rarer) galactosemia.

In 1961, President John F. Kennedy (whose sister Rosemary was mentally retarded) announced a major federal initiative. He promised to double the amount spent by the National Institutes of Health on retardation research, and appointed a Presidential Advisory Commission on Mental Retardation, charging it with appraising the adequacy of existing programs in the field. The Commission included major proponents of the scientific approach to the prevention of retardation and their perspective was reflected in its 1962 recommendations. Thus, newborn screening programs were characterized as an "important" step in preventing mental retardation and their expansion was recommended, even though the only screening experience at this time involved the unsatisfactory—and for that reason, generally discarded—ferric chloride urine test.[38]

The Commission also hired the Advertising Council to publicize the magnitude of the problem of retardation (an effort financed jointly by the Department of Health, Education, and Welfare and the Joseph P. Kennedy Foundation). The Advertising Council mounted a dramatic campaign advocating that the new PKU test "should be a must for all babies everywhere."

Lamenting that only Massachusetts, New York, Louisiana, and Rhode Island mandated testing, the ads compared the 50¢ [unit] cost of the test with the $100,000 required for lifetime care of institutionalized victims of the disease, and asserted—without any supporting evidence—that with a special diet, "a PKU baby then grows and develops as normally as any other child." They also urged citizens in states without legislation to demand that their states make testing of all infants compulsory.[39]

A member of the Children's Bureau staff protested futilely that "the proposals seemed in advance of general medical readiness" and went well beyond the recommendations of the Academy of Pediatrics.[40]

Even before the field trial had ended, the Guthrie test was being hailed as a major discovery, with the potential to reduce both the suffering and the financial burden associated with the disease. In numerous newspaper and magazine articles, it was described as an achievement with a potentially vast impact on mental retardation—though in the U.S., universal newborn PKU screening identifies fewer than 400 cases each year.

Screening was even promoted as a means to reduce overcrowding in institutions for the mentally retarded. After noting that there were approximately 5 ½ million mentally retarded individuals in the United States, Senator Joseph Montoya asserted that: "Many of these are a result of phenylketonuria and their mental retardation could have been prevented if detected in infancy. Most of the State training schools for the mentally retarded are overcrowded and have long waiting lists for admission".[41] However, it had long been known that PKU was the cause of retardation in less than one percent of institutionalized patients [42] and a 1962 Children's Bureau census had identified only 399 children with PKU admitted to programs for the mentally retarded during the preceding five years. The relatively few beds once occupied by patients with PKU would certainly be filled quickly with other severely impaired individuals.

Even commentators who acknowledged the rarity of the disease often considered screening a breakthrough, for they viewed it as a model for the prevention of other diseases. "The ailment is rare, but its importance is not to be measured in terms of numbers alone," wrote Harold Schmeck Jr. in the *New York Times* of May 21, 1961, explaining that its primary value was as a model for elucidating the causes of other disorders, especially those causing mental deficiency. The significance of PKU was often implicitly equated with the significance of mental retardation. In a typical passage, a writer for the *Family Weekly* noted that PKU "strikes only one child in 20,000. But circumventing this disease has opened a way toward eradicating the blight of mental retardation which, in the United States alone, afflicts 5,500,000 persons."[43] Guthrie himself argued that "the conquest of PKU is important not only for itself, but because it serves as an open door to a whole new era of preventive medicine based upon new understanding of medical genetics" (quoted in *Parents' Magazine,* Nov. 1995, p. 108). Contemporary assumptions concerning the potential impact of the Guthrie test were reflected in the American Medical Association's 1962 year-end report, which cited it (along with the unraveling of the genetic code) as a major medical breakthrough.

In the 1960s, it was assumed that early dietary treatment of some form would prevent complications in most other inherited metabolic disorders and some writers assumed it would prevent other forms of mental retardation and/or mental illness. Referring to galactosemia, cystic fibrosis of the pancreas, glycogen storage disease, and idiopathic hyperlipemia, one author wrote: "These diseases can now be readily diagnosed and controlled by changes in diet."[44] Another

explained that the discovery of an organic cause for PKU "suggests that, in time, certain other mental ailments—including schizophrenia and manic-depressive psychosis—may be found to have similar roots.[45]

Bolstered by this confidence in the efficacy of dietary treatment for many disorders, newborn screening initially appeared a much more powerful tool in combating retardation than, unfortunately, it turned out in practice to be. Readers of *Good Housekeeping* (Feb. 1966, p. 177) were assured that if dietary therapy were begun early enough, "a child will develop to his full mental potential." But in 1966, no one could possibly know if this claim were true. Relatively few early-treated infants had reached an age when their adult cognitive functioning could be predicted.[46] In 1965, a committee of the American Academy of Pediatrics noted that since an adequate diet had only become available in 1958 and early screening tests into general use after 1960, only a few individuals had been diagnosed with PKU within the first month of life, and "even they have been treated for less than six years, and this period of time is inadequate for assessing child development and projecting eventual intellectual ability on optimum treatment."[47] In addition, the developmental tests administered to infants and young children emphasized sensory and motor skills, not verbal and conceptual ones.[48] These tests could only be very imperfect instruments for predicting infants' ultimate intellectual achievement.

SKEPTICAL VOICES

As the above discussion suggests, there were also skeptical voices—some loud and some muted. One of the most vocal and extreme of the scientific critics was biochemist Samuel Bessman. Some of his concerns were shared by more circumspect colleagues, but he also argued, contra the scientific consensus, that the intelligence of "many" individuals with PKU would be normal without any treatment; that the apparent benefits of dietary therapy could well be attributed to placebo effects, and that the abnormalities associated with the disease were more likely to result from a deficiency of tyrosine than an excess of phenylalanine.[49,50,51]

Howard University political scientist Joseph Cooper was another emphatic critic. He publicized Bessman's views in articles, lectures, and testimony at legislative hearings, but he spoke for himself, rather than Bessman, when he charged that the emphasis on scientific prevention would deflect attention from much more pressing problems of the mentally retarded.[52,53] Noting that the vast majority of mentally retarded individuals did not suffer from PKU, or indeed any genetic defect, Cooper argued that their greatest need was for social support, not science. "What are we doing," he asked, "about the home-situated retardees who awaken one day to find that their parents or relatives are gone or no longer able to care for them? What do we do about these people? They must certainly outnumber those with PKU."[54] (Paul Edelson has argued that screening did indeed have the effect of moving social policy away from the provision of educational and social services to scientific prevention—a way of framing the issue that had little, if any, relevance to the vast majority of mentally retarded Americans.[55])

Most PKU researchers, including Bessman, focused on a narrower set of issues. One issue concerned the sensitivity and specificity of the Guthrie test. It was originally assumed that the results of Guthrie blood testing would be compared with later, more definitive tests. Guthrie himself suggested that tests be run both on the blood collected in the hospital and on urine-impregnated filter

papers, which the mother would mail back to the laboratory when the infant was 2 to 3 weeks old. He assumed that this method would avoid frequent false positives,[56,57] but the follow-up urine test soon proved unsatisfactory.[58,59]

The consultants to the California state health department expressed reservations shared by many researchers when they complained that data submitted on the Guthrie test were inadequate for determining either its specificity or sensitivity and expressed concern that some infants with confirmed high phenylalanine levels at 2 to 3 weeks might not require dietary treatment. Eight of nine consultants agreed that, although the test promised to be much more satisfactory than the ferric chloride test, "it requires further evaluation and our knowledge of PKU needs to be more complete before mass trials on the basis proposed by Dr. Guthrie would be justified." The consultants concluded "that more effective studies and approaches to PKU and screening procedures could be conducted by focusing on high risk populations and by more intensive studies in several areas as contrasted to deploying practically all available resources in a mass Guthrie Inhibition Assay screening procedure."[60]

The first systematic effort to assess the accuracy of the test did not appear until 1974. It reported that about 10 percent of infants with PKU were being missed by screening (either because they were not tested or because the test did not detect PKU), while only 5.1 percent of presumptively positive screening tests were confirmed as "classical PKU" (defined as a blood phenylalanine level of 20 mg/100 ml or more) on retesting.[61]

Guthrie had considered false positives a "small cost" in comparison with the benefit derived from early detection. That conclusion reflected a common assumption (now as then) that the costs in time, money, stress, and possibility of unneeded treatment are much less significant than the harm due to missed cases of the disease. On this assumption, screening tests should be oversensitive, so that all true cases are identified. "Although false positive tests [for inborn errors of metabolism] are acceptable within defined limits," wrote Harold Nitowsky, "there should be no false negative tests."[62]

Initial screening positives were confirmed with column and paper amino acid chromatography, the fluorimetric assay for phenylalanine, or a second Guthrie blood test (the last allowing the test to be its own criterion for accuracy) although Guthrie himself stressed that a positive Guthrie test "should be confirmed by repeated tests upon new blood specimens, and also by at least one independent method of determining blood phenylalanine."[63]

Testing uncovered many more apparent cases of PKU than would have been predicted on the basis of studies of the institutionalized mentally retarded. Studies of populations of retarded patients seemed to indicate that the frequency of PKU was between 1 in 20,000 and 1 in 25,000 individuals of European ancestry. But the results of Guthrie testing in Massachusetts indicated that it was actually about 1 in 14,000. Mabry, Nelson, and Horner argued that some part of the discrepancy was explained by hyperphenylalaninemic infants who were not retarded.[64] But while it was evident to most researchers that elevated blood phenylalanine levels could result from conditions other than classical PKU, no one knew what proportion of these individuals were actually at risk of retardation.

The problem of variant forms led to enormous confusion in the interpretation of elevated blood phenylalanine levels in newborns and its subsequent treatment. Guthrie and many pediatricians continued to believe that anyone with a slight but persistently above-normal phenylalanine level was at risk for retardation. But Berman, *et al.* found that older siblings of infants with elevated blood phenylalanine under 20 mg/100 ml levels also had moderate elevations

but normal mental development.[65] Most researchers argued that infants with moderate elevations were at no risk for retardation and should not be treated. In 1980, O'Flynn *et al.* found that 20 of 195 infants with markedly elevated phenylalanine levels on screening had variant forms that probably did not require treatment.[66] (But for recent challenges to the view that moderate elevations of phenylalanine are safe, see Guttler *et al.* 1993[67] and Diamond 1994.[68])

Uncertainty about who needed to be treated led to concern that some infants without PKU were being damaged by the diet. Some researchers believed that little harm would come from treating such infants. Woolf believed that twice as many patients were being treated for PKU as might be necessary but considered the financial cost, need to adhere to an unpalatable diet, and danger of dietary deficiencies "a small price to pay for preventing the mental deterioration otherwise inevitable in at least half of them".[69] Others thought that unnecessary treatment could itself produce mental retardation.[70] Several reports of deaths and diet-deficiency syndromes suffered by infants on PKU diets led researchers also to fear that some infants with the disease were being harmed by too-drastic treatment or suffering severe malnutrition as the result of diet refusal.[71] Problems in dietary management were compounded by uncertainty over the optimal level of phenylalanine and the exact phenylalanine content of foods and by the unpalatability of the special diet.

Moreover, there was no consensus as to how long treatment was needed. Some researchers assumed that only infants and young children needed to maintain the restricted diet.[72] They thought that when gross brain development was complete (around the age of five), it would be possible for children to eat normally. Others thought that therapy should be continued longer, even through adolescence.[73,74]

In articles and reports intended for nonspecialists, the more optimistic assumption was often presented as undoubted fact; the public was told that children could be taken off the diet by the age of five or six "for no further damage can occur once the brain is fully developed".[75,76]

Skeptical researchers also noted that intensive social and psychological support services would be required if dietary therapy were to be effective and predicted that these problems would be exacerbated if it turned out that the diet had to be maintained beyond early childhood. In short, they argued that too little was known about the nature of the disease, the reliability of the test, or the efficacy of treatment to justify compulsory screening.

Proponents, on the other hand, noted that, prior to the enactment of mandated screening laws, some states had low levels of participation and they argued that, in respect to the others, missing even one child was too great a cost. While generally conceding that there were many unknowns in the diagnosis and treatment of PKU, they maintained (in the words of Robert MacCready, Director of the Massachusetts Public Health Department and Chair of the Public Health Committee of the NARC) that "just as we must go into the water to learn to swim, we must continue to search out, treat, and study the phenylketonurics." They also stressed the importance of PKU screening as a "breakthrough prototype," asserting that it was "bound to progress toward control of the other inborn errors of metabolism associated with mental retardation."[77]

But even within the Children's Bureau, concerns mounted that screening might have been routinized prematurely. Bessman's claim that once legislation and fear of malpractice suits had combined to make treatment universal, it would be difficult and perhaps impossible to learn the answers to important scientific questions, resonated with some researchers. Members of the Bureau's Ad Hoc Committee on Medical Genetics reflected this concern when they suggested "that

alternate cases of tyrosinemia be treated to learn whether there is value in therapy before medico-legal problems, which have arisen in PKU, prevent an objective and scientific evaluation of the treatment of this metabolic disease also."[78] (On discussions concerning mass screening for tyrosinemia and also Wilson's disease, see Swazey 1971).[79]

A very small randomized clinical trial (RCT), in which only seven infants did not receive the special diet, would have sufficed to establish its efficacy.[80] But it was impossible to mount such a trial given the claims of benefit. (Although RCTs are more popular today than they were in the 1960s, most bioethicists consider withholding a treatment considered efficacious by a majority of researchers to violate the principle of "equipoise."[81]) In 1967, the Children's Bureau funded, as an alternative, the United States Collaborative Study of children treated for phenylketonuria (PKUCS)—a project that involved nineteen centers across the U.S. in following (originally) 224 infants diagnosed with PKU as a result of newborn screening. The PKUCS represented a systematic effort to investigate the effectiveness of dietary treatment by treating all infants, but to varying degree. It demonstrated that the diet was adequate for normal physical growth, could result in near-normal levels of intelligence, should be maintained throughout childhood, and that the most important factor in predicting IQ was the age at which the low phenylalanine diet is begun.[82]

SCREENING IN PRACTICE: A BRIEF SUMMARY

Initial problems of high false negative and very high false positive rates and unreliable laboratory work were eventually solved. But all the initial assumptions about the ease and effectiveness of therapy turned out to be much too sanguine and new problems emerged. The literature on cognitive and neuropsychological outcomes is vast: what follows is a very brief summary.

While nutritional therapy prevents retardation, intellectual deficits and psychosocial problems are common. Even early and well treated individuals with phenylketonuria often have lower IQs than would normally be expected and may experience other deficits; these include learning disabilities, visual/motor difficulties, increased emotional lability, agoraphobia, and thought disorders.[83,84,85,86,87,88,89,90,91] As a consequence, individuals with PKU often require long-term medical, social, psychological, and rehabilitative services.

The most serious deficits result from failure to maintain strict dietary control. Studies eventually revealed that IQ scores declined after the diet was abandoned; as a consequence, dietary recommendations became progressively more conservative. According to Virginia Schuett, recent reports prove that "high blood phenylalanine levels are not safe for anyone; they never have been, they never will be."[92] While not everyone agrees with the need for "diet for life,"[93,94] most treatment centers in the U.S. now do recommend lifelong continuance—a goal that is not easy to achieve.

DIETARY MANAGEMENT

Many accounts of screening assume an inevitable bridge between diagnosis and treatment. However, strict adherence to the diet is extremely difficult to achieve, especially in adolescents. The PKU diet involves phenylalanine-free or reduced substitutes for most natural protein foods, including bread, cake, meat, fish, eggs, and dairy products[95] supplemented by a formula with extra tyrosine and

other amino acids, vitamins, and minerals. For a number of reasons, most individuals with PKU (and their families) find the diet extremely taxing and few fully comply with it.

The formula is unpalatable, both the formula and special phenylalanine-free foods are burdensome to prepare, and the diet as a whole is boring. Adhering to it requires considerable motivation and skill. Even generally high-functioning individuals with PKU often suffer from math deficits, which makes diet calculations difficult. The formula and special foods are also expensive—roughly $5,000 per year for the formula alone.

Unfortunately, there are few studies of who pays for the diet therapy and how. We do know that there is tremendous variation in the quality and extent of services provided (as expected in state-based programs). However, while forty-three states had passed screening laws by 1975, none mandated treatment. Even now, many states neither provide treatment nor require insurers to reimburse for it.[96] Some states require reimbursement for treatment for PKU but not for other metabolic disorders; some provide for treatment "where practicable" or if the budget allows.[97]

In the early years of the program, the states generally subsidized the formula for infants and children (and continue to do so) and children were generally taken off-diet at the age of five or six. Moreover, the formula was originally classified as a drug, and was reimbursable for those with health insurance. When it lost this status in 1972, many insurers came to treat it as a food and refused to reimburse. At the same time, adolescents and even adults were increasingly advised to remain on-diet. While some states have passed laws requiring insurance companies to pay for the diet, self-insurers, who provide at least half of employee health insurance, are exempt from state laws under the Employee Retirement Income Security Act.

A study of the situation in New York, based on the experience of patients at three metabolic disorders treatment centers, is discouraging. Although half of the patients were covered by private health insurance and a quarter by Medicaid, most were unable to obtain reimbursement from these sources. The author writes: "The centers reported that many families considered the cost of these special foods to be a major burden. Their staffs interceded for patients by appealing to private insurance carriers and to local Medicaid offices to attempt to reverse decisions which had denied reimbursement for special foods. They reported that their efforts were rarely effective."[98]

In general, insurers have little knowledge of PKU (or any rare genetic disorder). Thus it is often necessary to explain, protest, provide extra documentation—a process that is especially wearing on families that already have problems coping with the disease.[99] Providers and health departments, who often make Herculean efforts to help, know that "the fact that effective therapy exists . . . does not mean that it is actually accessible to the children who need it."[100]

Even without the financial problems of supplying the diet, there are difficulties with compliance. Food is integral to religious and ethnic identity—which explains why immigrants' food habits are the last to change. Eating the same foods is one way of showing that we belong to a group.[101] Not surprisingly, women with PKU find it particularly hard to cope with holiday celebrations, which are frequently linked to religious and ethnic identity and often focus on food.[102]

Most important, meals express friendship and are used to establish intimacy.[103] Individuals who must avoid common foods face profound barriers to eating with others. They find it awkward to explain their dietary restrictions, know from experience that even if they do, people sometimes forget and they will be served something they should not eat, and that their friends and relatives will

often assume that it's fine if you only eat a little of the restricted food item. These difficult choices and embarrassing situations are particularly hard on adolescents, who are insecure and especially susceptible to advertising and peer pressure.[104] In the literature on insulin-dependent diabetes mellitus, there is a consensus "that adolescents as a group display the worst metabolic control."[105] Indeed, the folk wisdom seems to be that no adolescent fully adheres to the diabetic diet—which is considerably less burdensome than the diet for PKU.

Moreover, noncompliance with all medical advice is in general more likely when treatment recommendations are preventive rather than curative and when they involve lifestyle changes.[106] For all these (and other) reasons, eating behavior is very resistant to change. When it comes to young women with PKU, that is an especially serious problem.[107] For if they do not resume the diet prior to conception and maintain it throughout pregnancy, the effects on their offspring may be catastrophic.

THE PROBLEM OF MATERNAL PKU

Infants born to women with PKU do not themselves usually have the disease. However, high concentrations of phenylalanine are teratogenic—and the phenylalanine circulating in the maternal blood of women with PKU easily crosses the placental barrier. As a result, the offspring of women with classical PKU who do not maintain good dietary control are at great risk of mental retardation and microcephaly (over 90 percent) and lower risk (12-15 percent) for congenital birth defects and other anomalies.[108]

It is not easy for anyone to stay on the restrictive diet, much less to resume it. It is especially difficult during pregnancy when it is also necessary to consume about 25 percent more of the formula. Moreover, even well-functioning women with PKU often do not know how to cook.[109] As Charles Scriver writes: "It is possible to normalize the maternal metabolic phenotype during pregnancy with benefit to the fetus, [but] the effort required to achieve these goals can be awesome."[110]

Before the advent of newborn screening, women with PKU were severely retarded and often institutionalized so that they bore very few children. Most young women today discontinued the diet during childhood and have not been followed for many years. Since their fertility is now nearly normal, screening has had the paradoxical effect of converting a rare occurrence into a major problem.[111] Indeed, all the social benefits of screening may be neutralized by the birth of retarded children to women who have ended the diet.[112]

The Maternal PKU Collaborative Study (MPKUCS), which began in 1984, identified 402 pregnancies; researchers found that few of the young women were on diet (101 had IQs lower than 80). There were so few preconceptually treated and well-controlled pregnancies when the study began that researchers were unable to determine whether the current diet provides for adequate fetal growth and development.[113]

There are also some grounds for optimism. The socio-economic status and intellectual ability of the women enrolled in the study have improved over time. There has been a significant drop in the number of teenage pregnancies. And more women are initiating the diet preconceptually.[114]

Today, it is commonly said that the problem of maternal PKU came to attention as a result of the screening's success.

In fact, there were efforts in the early 1960s to focus attention on the potential problem. A report of three mentally retarded (nonphenylketonuric) offspring born to a woman with PKU appeared even before mass screening began[115] and in 1963, higher profile warnings appeared in *The New England Journal of Medicine*[116] and the *Journal of Pediatrics.*[117] Other discussions followed.[118,119,120,121]

But neither these discussions nor an editorial in the *New England Journal of Medicine*[122] had much impact. Legislators were surely unaware of the issues; indeed, in some states, screening laws passed by acclamation or voice vote and without either hearings or floor debates.[123] Robert Guthrie tried to prompt the Children's Bureau to action but even he was unsuccessful. Ironically, one reason seems to have been staffers' determination, in light of earlier experience, not to act prematurely.[124]

SCREENING FOR OTHER METABOLIC DISORDERS

Because PKU is such a rare disease (whose incidence also varies with ethnicity), some early screening programs identified few, if any, cases. Thus, in the first three years of the Washington, DC, program, no infants with PKU were identified and officials reasoned that they had better things to do with their money. Some other jurisdictions threatened to follow Washington's example and end their programs. The paucity of cases combined with problems that emerged in the first years of screening prompted a reappraisal of the value of screening programs.

One response was to load more tests on the original. By the end of the 1960s, a variety of other rare metabolic disorders were being detected with the same filter paper blood specimen employed for PKU screening. Most of these disorders could not be treated as effectively as PKU and at least one (histidinemia) was benign.

In the 1970s, a number of efforts were made to appraise the early history of PKU screening. All drew a similar lesson: there should be no rush to new screening programs. Thus, a committee of the National Research Council urged legislatures to avoid "*ad hoc* responses to pleas for state involvement in the increasing number of conditions for which screening will become available".[125] Harold Nitowsky spoke for many analysts when he wrote:

> I believe that we shall be forced to the conclusion that our knowledge of the natural history and variability of PKU is incomplete, that the effectiveness of treatment of the disease has not been accurately measured, that we have inadequate information about the optimal age for institution of dietary therapy, or the levels of serum phenylalanine (PA) at which treatment should be undertaken, or the age at which treatment may be stopped. Despite these unanswered questions, and the obvious lack of adequate validation of prescriptive screening, I do not believe we should turn backwards. . . . However, the lessons we have learned from our experiences with this disorder should serve as a warning against any impulsive or premature extension of prescriptive screening to a variety of other inborn errors of metabolism which are associated with serious illness or mental retardation, and for which screening tests are available as well as the possibility of dietary control.[126]

In spite of such warnings and more formal statements of principle, new tests were added without even the degree of pilot testing to which the Guthrie test was subjected. Newborn screening is administered by the states, so the testing programs vary tremendously. Today, all states test for PKU and for congenital hypothyroidism, while 42 test for sickle-cell anemia and 38 for galactosemia. Only five test for tyrosinemia, three for cystic fibrosis, and two for toxoplasmosis. In general, the new tests have been added casually, with little systematic assessment of their value and risks, and also with little concern for obtaining informed consent.[127]

A NOTE ON COST-BENEFIT ARGUMENTS

PKU screening had originally been made mandatory partly out of concern that voluntary programs might cease to be cost-effective. Advocates stressed the financial benefits, and used cost-benefit arguments to bolster them. In the 1960s, such analyses often compared the expense of laboratory testing and evaluation and of treatment with the assumed expenses to the state of providing institutionalized care (typically for 20 or 25 years) for a portion of the affected infants and medical and hospital costs for those not institutionalized. The "expense of laboratory testing" was sometimes equated with the unit cost of the test rather than the cost of the program to identify one affected individual—perhaps because the latter would include the cost of retesting the large number of false positives that is involved in all screening for very rare conditions.[128]

Well into the 1970s, simplistic claims abounded. The following passage from a 1977 NIH publication is typical:

- PKU...occurs approximately once in every 14,000 births.
- Screening newborns for the disease costs $1.25 per test; thus, approximately $17,000 is spent to detect each case.
- An additional $8,000 to $16,000 must then be spent for dietary treatment over a 5 to 10 year period, to prevent the retarding effects of the disease. This brings the total cost of prevention to about $33,000 per child.
- Untreated, severe mental retardation care for, say, 50 years in an institution at a cost of $20 a day, would run to $365,000, more than 10 times the cost of prevention.
- Add to this saving the input from the treated individual through earnings, taxes, and family and societal contributions.
- Such figures must be convincing, for 48 states now require screening of newborns for PKU and other genetic diseases.

While no reputable econometric study would make such claims, the NIH report reflects the reasoning that informed many cost-benefit arguments, especially those aimed at the public and at federal and state legislators.

Such analyses ignore the distribution of costs among the various payers, and aggregate all of them, whether costs are assumed by individual families, insurers, or the state, although the cost burdens may vary widely. They do not take into account indirect and intangible harms, such as the anxiety produced by false positive tests, the stresses on families of managing the restrictive diet, and the costs associated with maternal PKU. Further, it is misleading to equate the averted costs of institutionalization for PKU with the average annual cost per institutionalized patient. Preventing

the mental retardation associated with PKU would produce no more than a one percent drop in the inpatient population. The costs of the institutions are mostly fixed, so such a small patient reduction is unlikely to lead to an equivalent cost reduction.[129,130]

Cost-benefit considerations have, in the past, contributed to the trend to add new tests. An additional test adds only a marginal cost, since the same system can be used for collecting and transporting specimens and recording and reporting results. Thus, as Charles Scriver noted, "screening tests with relatively low yield can be included economically in such programs."[131]

This is not to imply that the costs of screening outweigh the benefits—on the contrary. A number of studies have shown that the cost to improve the outcome of PKU by screening and early treatment is comparable to other widely-used and accepted programs to prevent diseases or their manifestations.[132] Moreover, there are other non-institutional costs associated with having a child with mental retardation, including anxiety, stress, and continued expenses for medical and social care, and many medical interventions bring new problems in their trains; PKU is hardly unique in that respect. But these remarks do suggest that some considerations have been systematically ignored, thus distorting the ratio of benefits to costs.[133]

CONCLUSION

The history of PKU shows that it is easy to exaggerate the ease and efficacy of treatment and to understate the costs. It was said that dietary therapy would be inexpensive, brief, and easy to manage. Unfortunately, it is none of these. PKU has turned out to be a difficult chronic disease. The American medical system is oriented toward curing acute illnesses, not helping people with chronic ones to live well. Thus, it is relatively easier to obtain access to expensive diagnostic tests than help with activities of daily living. Assistance with such ordinary requirements is what many individuals with PKU need to function in their communities and to adhere to the diet. In maternal PKU, the amount of social support better predicts compliance with the diet than does IQ or knowledge.[134] Thus, effective treatment requires a focus on matters that lie outside the conventional bounds of medicine. PKU programs have come to pay much attention to the process of managing infants, children, and young adults, including pregnant women. That is presumably one reason that teenage pregnancies are down and IQs up. And it is a very important development. But as Friedman *et al.*[135] have recently warned, "unless adequate services and insurance to cover care of these pregnancies is firmly established, the ominous prediction of Kirkman" [who warned that all the gains of screening could be erased by the birth of infants to women with untreated PKU][136] may still come to pass.

Further, this history shows that once newborn screening programs became established, they may be rapidly routinized and, once routinized, easily expanded for other purposes. Human metabolic researchers had reservations, but with few exceptions, kept them to themselves. Even when they voiced doubts, it did not slow the approval of the screening programs. Thus, legislators heard only a chorus of good news. The newspapers and magazines they read made screening appear a major breakthrough in the battle against mental retardation, one that would be followed by prevention of other disorders. No wonder that, in most states, screening laws were passed without dissent—and that it was (and is) extremely easy to add new tests, even for diseases less treatable than PKU and after even less rigorous processes of validation.

Thus, a "technological imperative"[137] has combined with unrealistic assumptions about benefits to drive the expansion of screening programs. The lesson that such wholesale expansion is unwarranted has been repeatedly drawn since the early 1960s. Surely it is time to heed it.

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ABOUT THE AUTHOR

Diane B. Paul is Professor of Political Science and Co-director of the Program in Science, Technology, and Values at the University of Massachusetts at Boston and Research Associate in the Museum of Comparative Zoology at Harvard University. She has been an Exxon Fellow at MIT, a fellow of the Wissenschaftskolleg zu Berlin, a Resident Fellow of the Humanities Research Institute of the University of California, and the recipient of grants from the National Endowment for the Humanities and the National Science Foundation. Any opinions, findings, and conclusions or recommendations expressed in this paper are those of the author and do not necessarily reflect the views of the National Science Foundation.

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