

Newborn Screening in North Carolina: The Evolution of Policy and Practice

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Abstract

Newborn screening policies in North Carolina are due to the efforts of skilled and knowledgeable state officials, clinicians, and scientists who are able to develop effective newborn screening procedures. A newborn screening that was developed in North Carolina is the first automated method for diagnosing phenylketonuria. This process was later adopted in many other states. The use of tandem mass spectrometry in newborn screening was also pioneered in North Carolina, and it is being used in an increasing number of states. Newborn screening is more than testing, however; follow-up and specialized care are essential. State-level policies should recognize the multiple links necessary to make newborn screening effective and efficient.

In 1934 Norwegian physician Asbjørn Fölling reported a pair of siblings with a disease we now call phenylketonuria or PKU. Left untreated, PKU usually affects brain development and leads to mental retardation.¹ The disease was soon recognized as an autosomal recessive disorder in which each sibling of an affected child has a 25% chance of being born with the condition. By the early 1960s an infant formula low in phenylalanine was marketed and showed promise, when begun early, of preventing mental retardation. In 1963 Robert Guthrie, a microbiologist at the State University of New York at Buffalo, published a blood test for detecting the disorder in infants soon after birth.² The test utilized blood spotted onto filter paper. A punch of the blood-spotted filter paper was placed on agar containing the bacterium *Bacillus subtilis* and a substance that made the bacteria dependent on phenylalanine for growth. Affected infants had a greater zone of bacterial growth around their paper disk than did unaffected infants.

Early Days

Along with concerned parents, Dr Guthrie lobbied the legislatures of various states to mandate the testing of all newborn infants for phenylketonuria. Many states passed the mandate in the 1960s and subsequent events justified the early detection of PKU through newborn screening. At that time, North Carolina was fortunate to have Dr Theodore D. Scurletis as chief of the Maternal and Child Health Section of the State

Board of Health. With input from Dr James B. Sidbury, Jr of Duke University; Drs George Summer, John Hill, and Harrie Chamberlin of the University of North Carolina at Chapel Hill; and others, Dr Scurletis urged the governor and legislators to go beyond a mandate and authorize adequate funds for a state newborn screening laboratory in Raleigh. Governor Terry Sanford appropriated \$52 000 toward the laboratory in 1964, and the legislature approved continued funding. The laboratory became what is now the Newborn Screening Laboratory in the North Carolina State Laboratory of Public Health. Before testing was mandated in North Carolina, Dr Scurletis recognized the value of informing medical personnel about the importance of screening, and in 1965 he undertook an educational campaign for physicians, nurses, and health department staff. As a result, North Carolina's compliance rate reached 97%, exceeding rates in some states with compulsory testing.

Legislative action benefited North Carolina's newborn screening initiative by providing additional funds that were seriously needed at the time. Funding in North Carolina is influenced by the fact that the Newborn Screening Laboratory has an all-volunteer advisory committee made up of physicians and scientists who are experts in the various disorders being screened and who are from the different North Carolina medical teaching centers. The committee, which includes the parents of affected children and a representative of the North Carolina Pediatric Society, meets several times a year. The practicing physician representative can relay concerns about problems

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with newborn screening as well as practice-related details about newborn screening.

North Carolina as a Leader in Newborn Screening Methods

In addition to proposing funding, Dr Scurletis encouraged the use of an automated test³ for detecting elevated concentrations of phenylalanine rather than Guthrie's bacterial method. The automated test was developed in the early years of automated analysis—an approach now commonly used in laboratory medicine—and seemed more advanced and accurate than the Guthrie test. North Carolina physician-scientists Drs John Hill and George Summer of the University of North Carolina at Chapel Hill created the test. In the early years North Carolina was the only state using this test. It was later adopted by many other states as well as by regions of Canada.

The second major breakthrough in newborn screening also had its origin in North Carolina. In the late 1980s investigators at Duke University, principally Dr David S. Millington and Dr Steve Kahler, began using powerful tandem mass spectrometry (MS/MS) to study blood spots of newborns and to screen for amino acid disorders. Dr Mohamed Rashed of Saudi Arabia developed an electrospray method⁴ that allowed samples to be processed more rapidly with MS/MS. After the feasibility of newborn screening with MS/MS was reported,⁵ the procedure began to gain general use.⁶⁻⁸ The International Society of Neonatal Screening awarded their 2006 Guthrie prize to Drs Millington and Rashed. The MS/MS method superseded the automated fluorometric method and is now being used in an increasing number of other states. Since MS/MS screening is a major component of so-called “expanded” newborn screening,⁹ North Carolina was once again at the forefront. The MS/MS method can detect a wide variety of inborn errors of metabolism, some of which are so rare they are found in North Carolina infants only once every few years. (See Table 1.) Of the disorders detected by MS/MS in North Carolina, only those having an incidence of 0.5 in 100 000 or higher are individually listed in Table 1. While some disorders are too rare to justify screening for them individually, MS/MS detects them with little additional effort, raising ethical and legal questions about omitting them from screening.¹⁰

The Issue of Priority

In many states parents vigorously lobby state legislators to authorize screening for a disorder affecting their own child. Such action, while understandable, can result in testing with insufficient regard to cost or benefit. Hypothyroid screening in North Carolina came about in part because a distinguished pediatric endocrinologist, the late Dr Judson Van Wyk, explained the need for hypothyroid screening to his local state representative

in 1978. The origin of state funding for galactosemia screening is not clear. But one story is that a bill was introduced by a state legislator after he read an article on the subject while waiting for a haircut. Congenital adrenal hyperplasia can take the potentially lethal salt-wasting form or the less severe virilizing form. Screening for the disorder in North Carolina was initiated by a laboratory manager who had successfully established a screening protocol in a previous position.

The 2006 Newborn Screening Fact Sheets^{11,a} from the American Academy of Pediatrics briefly describe the disorders listed in Table 1 (and certain others) and include information on incidence and screening. In North Carolina, as in other states, the introduction of a test has not necessarily correlated with the prevalence of the disorder. Congenital hypothyroidism is over 10 times as common as PKU, also causes preventable mental retardation, and is easier to treat than PKU; however, testing for it was introduced after the PKU test. (See Table 1.) Screening for hemoglobinopathies was limited to infants of African American descent when introduced in 1987, although hemoglobinopathies can be present in other infants. Universal screening did not begin until 1994. Detection and treatment of galactosemia soon after birth can prevent cataracts, liver damage, and death but does little to prevent the moderate developmental disorders that occur. Screening for hearing impairment, which appears to be the most prevalent disorder, is on the basis that early intervention allows the affected infant to develop nearly normal speech, but this claim needs to be confirmed.¹¹ Figures for North Carolina are not yet known, but national surveys for this test indicate that the false positive rate is high and the follow-up rate is low.¹¹ For tracking of tests results to occur, a very serious need exists nationally¹¹ as well as in North Carolina for funding and policies that allow integration of hearing screening with ongoing programs of newborn screening and follow-up.

Prioritizing can be more complex than might be appreciated. As shown in Table I, biotinidase deficiency is rare, yet the extremely low cost of treating this potentially debilitating condition offsets its rarity. Congenital hypothyroidism and PKU have two features in common: both produce mental retardation if untreated in childhood, and both require management through adulthood. Considerations of the vulnerability of the developing brain led to the possibility that the costly phenylalanine-restricted diet of the child with PKU might be discontinued at age 4.¹² Subsequent experience revealed that discontinuing the diet caused the patient with PKU to have irritability, mood disorders, and a risk for seizures. Moreover, it is important for the woman with PKU to have her diet closely regulated during each pregnancy. Since high blood phenylalanine concentrations interfere with development of the brain in children with PKU, it is easy to understand why the same will occur with the brain of a fetus of a woman who has a high blood phenylalanine concentrations (even though the infant of a woman with PKU usually will not actually have PKU). Without treatment of pregnant women

a Fact sheets are available with updates, at <http://www.pediatrics.org/cgi/content/full/118/e934>.

Table 1.
Disorders for Which Newborn Screening is Provided in North Carolina in 2007

Disorder	Date testing started in NC	Confirmed cases per 100 000 newborns*
PKU	1966	See MS/MS
Congenital hypothyroidism	1979	49.7 ^a
Hemoglobinopathies	1987 & 1994	83.4 ^a
Galactosemia, classical	1988	1.6 ^a
Galactosemia, variant	1988	3.4 ^a
Congenital adrenal hyperplasia	1989	4.3 ^a
Hearing impairment	2001	146 ^b
Biotinidase deficiency	2004	0.5 ^c
Detected by MS-MS	1999	25.6 ^d
<i>Amino acidopathies</i>		
PKU		3.7
Hyperphenylalaninemia, not classical PKU		2.3
Citrullinemia		0.6
<i>Organic acidemias</i>		
3-methylcrotonyl-CoA carboxylase deficiency (3-MCC def)		2.9
Glutaric academia type 1		1.1
Methyl malonic acidemia		1.0
Isovaleric acidemia		0.6
<i>Fatty acid oxidation defects</i>		
Medium chain acyl-CoA dehydrogenase deficiency (MCADD)	7.6	
Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD)	1.4	
Short-chain acyl-CoA dehydrogenase deficiency (SCADD)		1.0
Disorders (12 such) with incidence less than 0.5 per 100,000		3.4

*These results, and inclusive dates, are from the North Carolina Newborn Screening Laboratory:

a 609,101 and 2002-2006.

b 363,974 and 2004-2006.

c 371,148 and 2004-2006.

d 930,321 and May 1999-December 2006. Of the infants in these MS/MS results, 81% are in the recent report⁸ of Frazier, et al

with PKU, the frequency of mental retardation (from maternal PKU) would equal the frequency of mental retardation in people with PKU before newborn screening and treatment was initiated.¹³ Thus, the total cost of managing PKU would seem to make it prohibitively expensive, yet the lifetime expense of the diet is less than the high cost of lifetime management of mental retardation or the costs associated with becoming unemployable.

Finally, early detection will not stop the ultimate progression of certain diseases but will provide opportunity to intervene and delay the onset of complications. Early detection also means the expense of unnecessary hospitalization and studies can be avoided. Examples of such diseases include sickle cell

disease and cystic fibrosis. Newborn screening for the latter occurs in some states and is under consideration in North Carolina.

State or Commercial Laboratory?

The campaign of Dr Guthrie and concerned parents for mandated PKU testing probably encouraged the screening of newborns to be conducted in state laboratories rather than private laboratories since the bacterial methods required by the original test are used there. In most states this served to prevent the privatization of newborn screening. Private laboratories made an effort in the late 1990s to introduce bills in various state

legislatures that would close state newborn screening laboratories and turn the activity over to commercial labs. At the same time the slowness with which many states adopt new screening methods prompted a discussion of the need for a national policy.¹⁴ Directors of state laboratories cannot act independently to regularly update methods and equipment but are often dependent on legislative appropriation and are slowed by bureaucratic red tape. The breakup of communist governments in Europe in the 1990s revealed the inefficiency of government operated services and made a case for privatization. In North Carolina some physicians and parents, unaware of the 1999 incorporation of MS/MS into the state program, sent samples to a private laboratory in another state.

The director of one private laboratory based in another state lobbied the North Carolina Pediatric Society to recommend closing the state laboratory and allowing his lab to do testing (including MS/MS screening) on a broader range of disorders. Members of the Society were unaware that this director had earlier visited Duke University to learn that MS/MS could be used in newborn screening. More critically, his suggested tests included detection of glucose-6-phosphate dehydrogenase deficiency, a disorder for which testing on newborn infants had been found inadvisable 35 years earlier, as was recognized by a member of the Newborn Screening Advisory Committee (appointed by the Newborn Screening Lab directors) who had authored over 20 articles on this subject. It must be conceded, however, that this laboratory provided 20 months of MS/MS screening under contract during development and confirmation of the MS/MS method in the state laboratory.

Remaining to be proven is whether privatizing newborn screening would result in lower costs. Many states now charge fees to support their state laboratories. In 1991 the North Carolina General Assembly authorized the North Carolina Department of Environment and Natural Resources to charge hospitals for testing. The charge was \$10 per initial test in 2002 and \$14 in 2005. The funds remain in the department to be used to support the Newborn Screening Program.

Screening and Follow-Up

Since the early days of newborn screening, the Newborn Screening Quality Assurance Program of the Centers for Disease Control and Prevention has been responsible for checking the accuracy of newborn screening laboratories in the United States. In North Carolina the extremely low rate of cases missed through laboratory error is due to the high quality of leadership within the Newborn Screening Laboratory. During many of the earlier years, the laboratory was under the capable direction of Maxine Matheson. As newborn screening became more technically complex, it was apparent the laboratory should be directed by someone board-certified in clinical chemistry, as has been the case for over 20 years.

The importance of an aggressive follow-up program became apparent in the early years of screening when 33 of 37 North Carolina infants detected as having PKU were promptly started on the low-phenylalanine diet. The 4 infants who were not placed

on a phenylalanine-restricted diet developed retardation,¹⁵ and several lawsuits were filed against physicians. None of these cases was the result of a laboratory error; all resulted from a breakdown in follow-up. This is in contrast to a national survey that revealed missed cases of PKU and hypothyroidism were more often the result of laboratory error than of failure to follow up.¹⁶

A system had evolved by 1974 for tracking abnormal results in North Carolina infants and seeing that each infant was either retested or referred for confirmation and treatment. That system was monitored by Elizabeth Moore, Genetic Program Manager of the Division of Maternal and Child Health. In the 1980s, during the period when MS/MS screening was contracted to a private laboratory, it became apparent that difficulty in coordinating follow-up was a potential problem. Another factor contributing to failed follow-up is a change in the physician of record when an infant is discharged from the hospital. A policy was finally established in North Carolina for laboratory staff to directly contact parents if repeat testing had not been obtained. This caused initial and understandable resentment among physicians until missed cases were documented. Despite the great importance of an effective follow-up program, the follow-up component is easily overlooked in funding of newborn screening programs.

The Issue of Who Will Manage Each Disorder

After an abnormal result from newborn screening, the confirmation and management of congenital hypothyroidism and the hemoglobinopathies (eg, sickle cell disease) may occur in many North Carolina medical teaching centers. In sharp contrast, the management of inborn errors of metabolism often requires specialized expertise. The dietary management of pregnant women with PKU, for example, is complicated by the nausea of early pregnancy and the changing metabolism of the pregnant woman. This situation is even more complex than that of the growing infant or child with PKU. Dietary management of many inborn errors of metabolism requires the expertise of a dietitian who has specific training and experience in managing such cases. Underrestriction can result in mental retardation or brain damage; overrestriction can result in death. Moreover, management of maple syrup urine disease, for example, requires regulating blood levels of three amino acids simultaneously.

In North Carolina, all PKU cases, approximately 90% of disorders detected by MS/MS, and certain inborn errors of metabolism are managed at the University of North Carolina at Chapel Hill by a dietitian who has a doctorate degree in biochemistry. This model of centralization also includes Duke University where confirmation and management of certain other inborn errors of metabolism occurs. This centralization is due to the difficulty of obtaining specialized skills in many locations. The disadvantage of centralization is the travel required of patients living elsewhere in the state. To offset this disadvantage, maximum use is made of mailed samples and telephone consultations. Although the Guthrie bacterial test is now seldom used, the method of collecting blood on filter paper (the Guthrie card) is ingenious and is widely used.

Guthrie cards have made newborn screening practical and have allowed North Carolina parents of infants and children with certain inborn errors of metabolism such as PKU to obtain samples for dietary monitoring and to inexpensively mail them to a laboratory. However, the cost of making available to needy families the expensive dietary formula and specialized care they require is a second area that is easily overlooked in funding newborn screening programs. The Guthrie card, incidentally, should not be called a "PKU card;" it is used to test for many more disorders than PKU. Until Dr W. Harry Hannon of the Centers for Disease Control and Prevention intervened in 1996, postal policies to prevent the transmission of HIV could have essentially put an end to newborn screening and subsequent dietary monitoring.

Current and Future Policies

Numerous considerations must be examined in developing policy on newborn screening. Little justification exists for screening for conditions that require no treatment until much later in life. It may be argued that the condition might be later missed, but such failure in later detection is a problem that must be addressed separately. The detection of some disorders must await technical advances that make screening reliable and relatively inexpensive. As newborn screening is extended to detecting more rare or less treatable conditions, testing becomes difficult to defend financially. Perhaps a standard should be applied that is unknown to newborn screening but familiar to other areas of public health. Will the dollars expended for the new screening prevent more grief and suffering than the same amount spent in other ways? Would funds be better directed to immunizations and accident prevention?

About 20% of current test samples need to be repeated because of an inadequate sample or borderline result. The introduction of screening for each new disorder inevitably leads to an increase in the total proportion of false positives, some of which can cause harm. A false positive for hypothyroidism or PKU is not as disturbing as one for galactosemia, which requires an immediate appraisal of whether the infant has septicemia, an early feature of untreated galactosemia. False

negatives are still worse. Thyroid deficiency is not necessarily excluded by results soon after birth. Some infants have enough thyroid function to carry them through early infancy but then later become thyroid deficient (especially infants with birth weights under 1 500 g). With extensive transfusions, a condition can be missed when the test is dependent on a blood protein (eg, biotinidase deficiency and the hemoglobinopathies). Physicians can decrease the number of false negatives by considering how the tests are done. High levels of metabolites in the affected infant occur largely after birth. With mothers and babies being discharged very early, a blood sample should always be obtained at discharge with an additional sample obtained by 1 week of age if discharge was before 24 hours. Infants on soy formula or total intravenous feedings cannot be diagnosed as having galactosemia from an elevated blood galactose and therefore require an additional assay.

Present techniques in DNA analysis are unlikely to simplify newborn screening since each disorder often results from any of many mutations. Moreover, the most common type of congenital hypothyroidism does not have a genetic basis. Of very great importance in newborn screening is the changing effectiveness of treatment particularly when early treatment is essential. It is possible that future bone marrow or stem cell replacements, for example, will make additional disorders appropriate for newborn screening. Krabbe disease¹⁷ and severe combined immunodeficiency¹⁸ are two disorders presently approaching this point.

Future policy should reserve decisions about future tests within the staff of the Newborn Screening Laboratory and their consultants. Printed policies for newborn screening can be obtained by calling the Newborn Screening Clinical Chemistry Unit at (919) 733-3937. **NCMJ**

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