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Minireview

Newborn screening: rationale for a comprehensive, fully integrated public health system

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Abstract

Newborn screening has existed for approximately four decades [1]. During that period of time, newborn screening has evolved conceptually from a laboratory test for a single disorder, phenylketonuria (PKU), to a multi-part public health system involving education, screening, diagnostic follow-up, treatment/management, and system evaluation [2–5]. At a time when newborn screening is recognized as a model for predictive medicine [6,7], it also faces critical challenges that will determine its future credibility and viability. In order to understand these challenges, it is helpful to review briefly the history of newborn screening.

Early phase: establishing newborn screening in the public health sector

Newborn screening arose from a confluence of ideas and occurrences. As a result of a persistent mother wanting to know the cause of her children's mental retardation and corresponding peculiar odor, Fölling identified phenylketonuria (PKU) as the cause and, in 1934, he reported a method for identifying its presence through a colorimetric chemical test for phenylpyruvic acid in urine [8]. In 1953, Bickel and colleagues showed that dietary phenylalanine restriction in patients with PKU could reduce their blood phenylalanine level and moderate their intellectual phenotype [9,10]. A few years later, in 1957, a diaper screening test based on Fölling's earlier work with urine was initiated in some California health clinics, but its utility as a screening test was found to be less than optimal [11].

Guthrie, a biomedical researcher who developed a simple bacterial inhibition assay (BIA) for measuring circulating metabolites in cancer patients, adapted the BIA to measure elevations of phenylalanine from dried blood absorbed into filter paper blotters [1,12]. At the time, he was involved with the National Association for Retarded Citizens (NARC) (formerly the National Association of Parents of Mentally Retarded Children) because of a son with developmental delay and a niece with PKU. After his test development, Guthrie became a "crusader" for universal screening of newborns for PKU and was instrumental in mobilizing NARC chapters for newborn screening advocacy at the state level. This vigorous "grass roots" political activity by NARC members contributed to passage of laws in a number of states mandating PKU testing for all newborns [4,13,14].

The remainder of this early phase in newborn screening history was characterized by a conceptual evolution that led to laws mandating newborn screening in most of the remaining states [4]. Initially, newborn testing was often fragmented, with individual hospitals and private laboratories performing screening

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for their local newborns. While intra-state laboratory testing fragmentation remained a problem in a few states until relatively recently, many consolidated newborn screening laboratory testing into state public health laboratories and regional testing centers during this early phase [15]. The reasons for this consolidation were several-fold: (1) phenylalanine was stable in the dried blood spots on filter paper, thus permitting samples to be mailed to remote facilities; (2) laboratory proficiency testing was believed to be better when samples from actual cases of a disorder were encountered within reasonable time periods [16]—a fact not easily accomplished in small-volume laboratories for PKU because of its relatively infrequent occurrence; and (3) integration of laboratory testing (analytic phase) and follow-up of positive screens including confirmatory testing and long-term management (postanalytic phase) were considered to be more efficient when combined and centralized [17].

Thus, the primary accomplishments in the early phase of newborn screening were the establishment of mass newborn screening for PKU from dried blood spots and the recognition that centralization of laboratory testing and follow-up permitted improved health service delivery as part of fulfillment of states' public health missions. Unfortunately, there is a legacy remaining from this initial phase of newborn screening that continues to interfere with communication of screening results in some states to this day. This legacy concerns the fact that PKU testing was the only newborn screening procedures performed in nearly all states for a period of a decade or more. Consequently, the newborn screen was commonly referred to as the "PKU test" or "PKU screen" by nursery and program personnel. All US programs now perform testing for at least three disorders, but in many venues newborn screening samples are still referred to as "PKU samples" and testing results as "PKU results" whether or not they actually concern PKU testing. As a result, we are aware of patients for whom definitive confirmatory testing for a screened disorder was delayed because a positive "PKU result" was reported, when, in fact, it was a positive result for another disorder. For example, for a patient who tested positive for galactosemia, a quantitative plasma amino acid analysis (to confirm PKU) was ordered and performed rather than analysis for galactose 1-phosphate uridyltransferase activity. Such miscommunications may not only delay confirmation, but, if not clarified, could lead to a final report of normal for all screened disorders since "PKU" would not be confirmed (since the patient's results would be misinterpreted as a presumed false-positive for PKU on initial screening, and confirmatory testing would remain undone). In such cases, the screened disorder might go undiagnosed until clinical symptoms occurred.

Middle phase: expansion of newborn screening testing panels

The second phase of newborn screening began in the mid-1970s and extended into the early 1990s. This phase was characterized by expansion of newborn screening to include not only PKU, but also a number of other disorders. While Guthrie had continued to develop bacterial assays for other metabolic disorders throughout the 1960s, and a few programs experimented with expanded testing, newborn screening programs did not really expand until the late 1970s after there were pilot data documenting the efficacy of newborn screening for primary congenital hypothyroidism (CH), a disorder five times more prevalent than PKU. Demonstration of testing efficacy was a direct result of technological advances that improved CH testing sensitivity at a lowered cost [18–20] and automated blood spot sample preparation [15].

Screening for CH involved expanding laboratory technology beyond the BIA to include immuno- and radiochemical methods. However, the radioimmunoassays (RIAs) and enzyme-linked immunosorbent assays (ELISAs) used were analytical methodologies familiar to clinical chemists in contrast to technologies added in the next phase (to be discussed later).

An important new concept of using "two tiers" of testing to improve specificity and reduce costs also developed as part of CH testing protocols. Two-tiered screening for CH in the United States developed using a combination of quantitative assays for thyroxine (T_4) and thyrotropin (also known as thyroid-stimulating hormone, TSH) [21,22]. In patients screened at 1–3 days with the typical form of CH due to thyroid gland dysfunction, circulating T_4 is decreased and TSH is correspondingly increased. At the time CH screening began, neither neonatal T_4 nor TSH testing alone was considered sufficient to provide acceptable screening sensitivity and specificity, and performing both tests on all samples was considered to be too expensive. By measuring one of the analytes, for example T_4, on all specimens, and then measuring the other (in this case, TSH) on samples with a T_4 result below a certain threshold value or percentile, an acceptably low false-negative rate could be achieved without an excessive false-positive rate. While there was no international consensus as to the best initial test to use for CH screening (T_4 or TSH), the majority of programs in the United States initially chose to test first for T_4 and with the second tier being TSH. This was primarily due to the fact that newborns were usually screened closer to birth in the United States and, therefore, higher numbers of falsely elevated TSH values were expected due to a physiologic TSH surge in the time period shortly after birth [23]. Additionally, screening first with T_4 allowed an additional benefit of detecting cases of secondary hypothyroidism, since these

patients have normal TSH levels and decreased T_4 and would not be detected in a program using TSH as the initial screening test. By using the two tests sequentially on the same dried blood specimen, screening sensitivity and specificity for CH was satisfactory. This concept of testing in tiers has now led to cost-effective screening for diseases that may otherwise have been delayed or avoided due to testing cost issues.

With the inclusion of CH testing, and the use of automated punching in newborn screening programs, additional tests could be more easily added to testing panels since the punching machines simultaneously punched and distributed four disks (samples) from a single dried blood spot. Thus, when a newborn screening program expanded beyond a single disorder, PKU, to a second, CH, and incorporated automated punching into its procedures, it was incumbent to consider adding other disorders in order to efficiently and completely utilize the four samples that were punched. Addition of tests that were inexpensive to run and required few or no new personnel were particularly appealing. Once a program exceeded four tests, it was logical to consider eight since the sample preparation step for another four tests was already accomplished.

Hemoglobinopathy screening was a popular choice for addition to screening panels by a majority of states during this period (also using a two-tiered approach) [24]. It was during this time period that a multicenter randomized clinical trial of penicillin prophylaxis among infants with sickle cell disease was terminated early because of deaths from overwhelming sepsis in the placebo-treated group but not in the antibiotic-treated group [25]. Based on the report of this experience, an NIH Consensus Development Conference on Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies was convened in 1987 [26]. The consensus conference panel concluded that newborn screening for sickle cell disease should be universal (as opposed to targeted) utilizing a centralized laboratory concept. Additionally, screening programs were instructed to participate in a comprehensive care program to ensure initiation of penicillin prophylaxis before 4 months of age. Over the next 3 years (1987–1990), approximately $12 million from the Health Resources and Services Administration (HRSA) was distributed to states to establish hemoglobinopathy screening in states needing supplemental financial resources [24]. It is important to note, that despite the strong, data-driven, and well-reasoned recommendation for universal neonatal sickle cell screening from a distinguished federal panel, such testing has yet to be implemented in all newborn screening programs. We will discuss the need for a national newborn screening agenda later. The experience with sickle cell disease screening illustrates the need, not only to arrive at a consensus on a national agenda, but also to have the resolve to implement that agenda.

Newborn screening testing expansion during this period of screening history occurred differently for each program. Some programs utilized expert advisory committees to consider addition of more disorders in a deliberate manner based on scientific criteria. Other programs added tests by a political process driven by influential citizens and government officials. As we will see below, the results of these different approaches have now resulted in tests and technologies that are widely discrepant among the US state and territorial newborn screening programs.

Most recent phase: broader expansion of diseases and technologies

The expansion of diseases included in newborn screening test panels continued throughout the 1990s to the present. The consequence of this expansion, which has varied dramatically across programs, has been the disparate protection of neonates by the public health system in different states and territories [7]. All states screen for PKU and CH, which can be attributed to the fact that these disorders drove the decisions in the first and second phases of screening. However, there is no other disorder for which newborn screening is currently mandated in every state. As a result, some states mandate as few as three disorders and others mandate more than 30 [6]. Some programs use technologies dating from the original work of Guthrie in the 1960s while others use highly sophisticated state-of-the-art technologies only recently available [4,5,7].

In 1999, the American Academy of Pediatrics (AAP) and HRSA cosponsored a Newborn Screening Task Force to consider these disparities and other issues and their report was published in 2000 [5]. Included in the Task Force Report was a recommendation that newborn screening must be viewed as an integrated system including preanalytic (e.g., education, informed decision making, sample collection), analytic (laboratory testing) and postanalytic phases (follow-up confirmation, diagnosis, treatment/management, counseling, program evaluation). Additionally, the Task Force called for a national agenda to identify a core group of disorders for which every US newborn should be screened and the appropriate technologies to be used in their screening.

The March of Dimes Birth Defects Foundation (MOD) responded to the Newborn Screening Task Force Report with a call for more rapid development of a specific screening agenda, with less emphasis on screening costs and more emphasis on screening benefits [27]. Other consumer support groups, such as Tyler for Life (http://www.tylerforlife.com) and the National Coalition for PKU and Allied Disorder (http://www.pku-allieddisorder.org), developed grass roots advocacy efforts in many states. These organizations,

independently and together with HRSA, the American College of Medical Genetics, and other individuals and groups are working to develop an appropriate national agenda for newborn screening [6].

During the 1990s, newborn screening possibilities and expansion continued using new technologies with which routine newborn screening and clinical chemistry laboratories had little or no experience. These screening technologies included molecular genetic methodologies and tandem mass spectrometry (MS/MS). Additionally, hearing testing technologies advanced to a point where hearing screening in the newborn nursery became viable.

In the mid-1980s, DNA was shown to be stable in, and extractable from, neonatal dried blood samples [28]. This DNA could be extracted and amplified by the polymerase chain reaction (PCR) or directly amplified without extraction from methanol-fixed samples [29–31]. Following demonstration of the potential applicability of DNA testing in newborn screening situations, a pilot program at the Texas Department of Health demonstrated that DNA confirmatory testing for sickle cell disease as a follow-up to initial screening, and using the same dried blood spot, reduced the mean age at diagnosis in half, from approximately 4 to 2 months of age [32]. Not only did this testing protocol (a two-tiered system using DNA testing as the second tier following routine isoelectric focusing) ensure that the majority of screened newborns received penicillin prophylaxis before 4 months of age, but also it drastically reduced the time and effort expended in patient follow-up and confirmatory testing. A second tier DNA analysis was also proposed for cystic fibrosis screening in 1990 [33], and was shown to be effective [34] and shown to be useful in decreasing unnecessary follow-up in newborn screening [35]. Second tier DNA testing has also been suggested for newborn congenital adrenal hyperplasia screening [36,37] and medium chain acyl CoA dehydrogenase (MCAD) deficiency screening [38,39]. The utility of DNA follow-up for hearing screening is also a subject of much discussion [7,40–42].

Early in the 1990s, MS/MS was also applied to newborn screening disorders, first as a pilot research project in North Carolina [43]. Its demonstrated utility and reduced operational costs has now led to broader incorporation and integration into newborn screening programs [44,45]. The sizable initial investment in equipment, the lack of experienced laboratory personnel trained in result interpretation, and the lack of a research mission in most newborn screening programs have been barriers to development of this technology in most states. As a result, supplemental screening programs have developed in the private sector [4]. There is serious concern that these private supplemental programs, if not integrated into the established newborn screening systems, will fragment these systems and will serve to further increase screening inequities on the basis of socioeconomic status.

During the 1990s, neonatal hearing screening developed in most states, often as completely separate programs discrete from previously established newborn screening systems, despite the fact that many of the service delivery issues are similar. Although newborn hearing abnormalities are much more common (1/500) [40,46] than the diseases identified by dried blood spot testing, the frequency of hearing loss is sufficiently low to be a challenge for individual hospitals. Hospitals are generally not prepared to operate the active follow-up system necessary to ensure that all positive screening tests receive appropriate confirmatory testing. Although the primary screen is a functional hearing test that is performed at the individual birthing hospitals [47–51], electronic analysis and communication would permit centralization of quality assurance and quality improvement (QA/QI) activities [48,52]. Additionally, increased confirmatory testing resulting from screening is placing significant stress on the audiologic services recommended for follow-up due in part to a lack of audiologists trained in newborn testing and diagnosis. Integration of neonatal hearing screening data collection efforts with newborn dried blood spot screening data already being collected across the country would provide a fast and efficient means of creating centralized tracking databases that could improve service delivery currently recognized as a major problem in these programs. Additionally, integration of these two programs would permit second-tier DNA testing and more rapid confirmatory diagnosis for the large portion of the group who fail their neonatal hearing screens and who have one of the common mutations for connexin-26 [7]. DNA detection methodologies for cytomegaloviruses, also considered a major cause of congenital hearing loss, using dried blood samples are also under development [53] and would also be facilitated by program integration.

Challenges for the future

All cultures are products of their own histories, the resources surrounding them, and their development, receipt, and acceptance of innovation [54]. Newborn screening represents an example of an extremely dynamic culture. In the course of 40 years we have experienced its growth from testing for a single disease to screening tests for well over 30 diseases. The technology has changed dramatically from a relatively simple microbiological assay to more complex molecular genetic and MS/MS methodologies that require sophisticated instrumentation and informatics, and highly trained personnel. Digital electronic approaches now permit efficient and direct communication between birthing

centers and the newborn screening laboratory, alerting the laboratory in advance to the anticipated arrival of a patient's sample. Testing results can be securely transmitted in turn to physicians via telefax or made available on automated voice response systems or on the Internet.

Forty years ago entirely new programs were set in place de novo and individual state infrastructures developed to support newborn screening over the ensuing years. While extremely varied, all states and territories have newborn screening systems [55]. A number of critical questions remain, however.

- Do the individual states and territories have the resources and the resolve to provide the menu of tests and technologies that will represent the consensus national agenda called for by the Newborn Screening Task Force [5], the MOD [27], or other professional groups that may work on this issue in the future?
- Will advocacy groups have the patience to work with current screening systems toward a national agenda or will they feel forced by inadequate and unresponsive systems to aggressive campaigns on the addition of specific diseases and/or technologies within individual states?
- Will the federal government provide support via HRSA—perhaps through Title XXVI of the Children's Health Act of 2000 (Public Law 106–310), as they have in the past, to help states expand their newborn screening systems?
- Will state newborn screening systems expand within the traditional public health arena, or will the private fee-for-service supplemental screening programs displace the states and force the development of a parallel nonintegrated program that may ultimately fragment and disrupt universally available newborn screening?
- What will happen to those without the ability to pay for newborn screening testing and services?
- Will the public become better educated regarding expectations from the newborn screening and force expanded newborn screening through increased lawsuits when a child with a disorder detectable through screening at birth goes undetected?

A parallel program has already developed in many states for newborn hearing screening. There are many lessons that can be learned from the history of newborn dried blood samples screening and applied to aid in rapid, efficient, and effective development of newborn hearing screening. Optimized newborn dried blood spot and hearing screening will likely require consolidation of some aspects of the program(s) into centralized state or regional systems.

- Will programs have the will and ability to achieve program integration or will politics and bureaucratic inefficiencies prevent it?

Significant new issues have arisen that must be addressed during the next period in the history of newborn screening. These include informed consent, privacy and confidentiality of DNA databases, and appropriate uses of stored specimens. Only one state, Maryland, has a newborn screening law that requires testing consent (opt in) by mandating that newborn screening be offered rather than required [56]. Others either have a policy of informed dissent (opt out) or are silent on this issue, frequently permitting a family to refuse screening only for religious reasons [57]. The most important consideration in any consent policy consideration is the adequacy of the information provided and the manner in which it is provided. Genetics education and shared decision making is an area that will require additional resources to improve preanalytic education of health professionals and families, and to study the best ways of providing that education. In the real world of 21st century medicine, with shrinking margins in healthcare and less time available for individual caretakers to spend with their patients, the sources for these additional resources will be difficult to identify.

The requirement for informed consent will have increased immediacy as we enter the new era of newborn screening with exciting opportunities for expanding tests and technologies. This expansion will require ongoing research and development. Many of the new disorders that will be added are genetic and there will be unanticipated consequences of such genetic testing, including previously unrecognized disease associations and genetic discrimination. The families of the newborns being tested must be fully informed to the best of our ability about the potential risks of participation in research using identified or identifiable specimens [58].

The demonstration that DNA is stable in dried blood specimens means that these specimens represent potential DNA databases [59]. Newborn screening systems must develop standard operating procedures (SOPs) to assure participants and their families that any samples on which identifiers are retained will be maintained in a secure manner to protect the individual's privacy and confidentiality, unless informed consent has been obtained for their use in research. In addition, SOPs must be developed to govern the appropriate use and reuse of samples. Since the samples contain the child's DNA, these specimens could be requested for forensic purposes, such as paternity testing or identification of remains from a missing child, or for testing of diseases not included on the newborn screening menu.

The challenges facing the newborn screening systems represent positive issues in the growth and development of this discipline. Newborn screening has moved from its infancy through the toddler stage to its childhood. Now this field faces an awkward adolescence with rapid growth and exciting opportunities. With continued care and broad community involvement, newborn screening will eventually enter adulthood. As a model for predictive

genetic medicine, newborn screening will be watched closely through this transition.

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