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Simple Test, Complex System: Multifaceted Views of Newborn Screening Science, Technology, and Policy

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Abstract

Newborn screening (NBS) is a public health service provided for all babies born in the United States and in most countries of the developed world. A series of tests are applied to the blood taken from newborn babies to detect genetic and metabolic disorders that can be treated if identified early. With early treatment and therapy, the affected babies can usually live a normal, healthy life. Timing for sampling, testing, and reporting is vital for NBS to function as an effective system. In order to be an effective system, the evolution of science, technology, and policy gradually had to come into a synchronous partnership, where the discovery of new genetic disorders led to timely development of technology for screening, which is supported by policy and implemented into practice. The timely "dance" of these partnerships in an era of personalized health and medicine forms the integrated approach supporting NBS. This review will include a brief history of scientific development, policymaking, and the economic consideration in the expansion of the NBS.

Keywords

newborn screening, policy, advocacy, economics, whole-genome sequencing

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Introduction

With timely diagnosis made as a result of newborn screening (NBS), the affected babies can be treated early on and thus can survive and, in most cases, thrive. Due to clinical, technical, ethical, and other considerations, not all disorders can be screened for, and not all programs screen for the same number of disorders, but nevertheless, NBS is considered one of public stories of public health.[1] The NBS system functions in a multifaceted environment of stakeholders (scientists, physicians, policymakers, bioethicists, parents, and government), with multiple-level processes (sampling, transportation, laboratory screening, diagnosis, follow-up, treatment, and education), and transdisciplinary fields involved (biomedical sciences, public health, and medicine). However, at the initiation of NBS, there was a lack of consensus for the number and types of disorders, the communication across the different stakeholders was not clear, and the strategic approach to communicate complex information was not well defined.[2-5] Thus, the role of policymaking, the involvement of stakeholders, and the emergence of screening technology gradually evolved, though not seamlessly, to create an effective NBS system offering to detect 35[6] conditions and many more in the future as technologies support. This article will discuss the evolution of policymaking, scientific discoveries of screening technologies, and the revised screening criteria to justify and support expanded NBS. Within the first 48 hours of their life, their long-term health journey is determined by a simple, rapid screening test using blood from a heel stick.[7] This journey is "newborn screening."

Newborn screening is a core public health service. Once identified through screening, genetic and metabolic disorders can be effectively treated or managed. With early treatment and therapy, the affected babies can usually live a normal, healthy life. Historically, not all

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disorders can be screened for, and not all programs screen for the same number of disorders.[2,3,8] To address some of this discrepancy, the federally supported advisory board for NBS was created to determine candidate disorders and recommend a minimum screening panel that would apply to all NBS programs. Currently, 35 conditions are in the recommended panel of screening disorders, including 9 organic acidemias, 5 fatty acids oxidation disorders, 6 amino acid disorders, 2 other inborn errors of metabolism, 2 endocrine disorders, 3 hemoglobinopathies, hearing loss, severe combined immunodeficiency, lysosomal storage disorders, congenital heart disease using pulse oximetry, and cystic fibrosis.[9-14] A recent addition (July 2018) was spinal muscular atrophy. Even though the effect of early treatment for some conditions is still being evaluated, some states have moved forward and are screening for lysosomal storage diseases, for example, Krabbe disease, Fabry disease, Gaucher disease, Niemann-Pick disease, and Hurler disease as well as adrenoleukodystrophy.[15-19] The Recommended Uniform Screening Panel (Tables 1 and 2) includes 35 core conditions and 26 secondary conditions (ie, disorders that can be detected in the differential diagnosis of a core disorder).

In the near future, next-generation sequencing technology may be offered as first-tier or second-tier genetic testing in NBS.[20] However, due to current high cost (estimated at between $1000 and $2000 for a genome sequenced with an approximate 26-hour turnaround time) and lengthy turnaround time on genome results compared with the current NBS test, the application of genome sequencing into full-scale NBS may not be in the intermediate future.[1,21-23] With the advancement of technology, genome sequencing may be affordable and conceivable with shorter turnaround time and higher testing sensitivity and specificity.

A Brief History of the Newborn Screening Policy

Policymaking in NBS is complex and requires stakeholder involvement. The decision to explore the "benefit potentials" of screening is made by parents, physicians, public health professionals, and elected officials. It is important to note that the neonate cannot voice consent whether to be screened or not screened, raising ethical questions.[24,25] Several key events occurred that resulted in a ripple effect to the expansion of NBS.

In 1998, Newborn Screening Task Force brought together agencies such as the National Institute of Health, Center for Disease Control and Prevention, the Agency for Healthcare Research and Quality, Genetic Alliance, and the Association of State and Territorial Health Officials, the Association of Maternal and Child Health Programs, and Association of Public Health Laboratories.[26]

In 2000, *Blueprint for the Future*, by the American Academy of Pediatrics, a document describing the complexity of the NBS, emphasizes transparency in order to have high efficiency and effectiveness throughout each stage of the screening process, from the sample collection of the heel stick, laboratory testing, diagnosis, medical management of treatment, and the long-term follow-up.[27] The March of Dimes began to publicly advocate for the support to uniform NBS. The list of recommended conditions grew from 10 to 29 and beyond, encouraging states to expand their testing programs in order to reduce health disparities and correct for unequal access to care.[28]

In 2005, the American College of Medical Genetics identified a list of the conditions for states to screen for, which became the Recommended Uniform Screening Panel; the list was subsequently endorsed by the Secretary's Advisory Committee on Heritable Disorders of Newborns and Children (SACHDNC). The working group consisted of experts in metabolic genetics and did not include experts in evidence-based medicine, bioethics, primary care, and health economics.[29] While the report was primarily a scientific evaluation, the information contained serves as policymaking vehicle to justify the expansion of NBS. As a result, the criteria for screening was revised to consider: (1) that the condition can be identified during the time (24-48 hours after birth) during which it would not be detected clinically, (2) that a screening test with appropriate sensitivity and specificity is available, and (3) that the potential benefits of early detection and timely intervention.[30]

In 2008, Newborn Screening Saves Lives Act of 2007 was passed by Congress and signed into law in 2008, providing grants for follow-up care, improvements in NBS education, advances in screening technology, training, and follow-up strategies, quality assurance, outreach, and coordination follow-up.[31] In 2014, an extension of the Newborn Screening Saves Lives Act of 2008 was signed into law, which includes "an amendment addressing research uses of newborn dried blood spots and requiring immediate new interpretations of the HHS regulations for the protections of human subjects effective 90 days from the enactment of the law."[32]

The Complexity of the Multiple-Stakeholder Decision-Making Process

Prior to 2005, each state determined the number and the type of condition the state program would screen for. At

Table 1. Recommended Uniform Screening Panel[a] Core[b] Conditions[c] (as of July 2018).

	Metabolic Disorder					
Core Condition	Organic Acid Condition	Fatty Acid Oxidation Disorders	Amino Acid Disorders	Endocrine Disorder	Hemoglobin Disorder	Other Disorder
Propionic acidemia	X					
Methylmalonic acidemia (methylmalonyl-CoA mutase)	X					
Methylmalonic acidemia (cobalamin disorders)	X					
Isovaleric acidemia	X					
3-Methylcrotonyl-CoA carboxylase deficiency	X					
3-Hydroxy-3-methyglutaric aciduria	X					
Holocarboxylase synthase deficiency	X					
β-Ketothiolase deficiency	X					
Glutaric acidemia type I	X					
Carnitine uptake defect/carnitine transport defect		X				
Medium-chain acyl-CoA dehydrogenase deficiency		X				
Very-long-chain acyl-CoA dehydrogenase deficiency		X				
Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency		X				
Trifunctional protein deficiency		X				
Argininosuccinic aciduria			X			
Citrullinemia, type I			X			
Maple syrup urine disease			X			
Homocystinuria			X			
Classic phenylketonuria			X			
Tyrosinemia, type I			X			
Primary congenital hypothyroidism				X		
Congenital adrenal hyperplasia				X		
S,S disease (Sickle cell anemia)					X	
S,β-thalassemia					X	
S,C disease					X	
Biotinidase deficiency						X
Critical congenital heart disease						X
Cystic fibrosis						X
Classic galactosemia						X
Glycogen storage disease type II (Pompe)						X
Hearing loss						X
Severe combined Immunodeficiencies						X
Mucopolysaccharidosis type I						X
X-linked adrenoleukodystrophy						X
Spinal muscular atrophy due to homozygous deletion of exon 7 in SMN1						X

[a]Selection of conditions based on "Newborn screening: toward a uniform screening panel and system." *Genet Med*. 2006;8(suppl 1):S12-S252, as authored by the American College of Medical Genetics (ACMG) and commissioned by the Health Resources and Services Administration (HRSA).
[b]Disorders that should be included in every newborn screening program.
[c]Nomenclature for conditions based on "Naming and counting disorders (conditions) included in newborn screening panels." *Pediatrics*. 2006;117(5 pt 2):S308-S314.

Table 2. ACHDNC Recommended Uniform Screening Panel[a] Secondary[b] Conditions[c] (as of July 2018).

	Metabolic Disorder				
Secondary Condition	Organic Acid Condition	Fatty Acid Oxidation Disorders	Amino Acid Disorders	Hemoglobin Disorder	Other Disorder
Methylmalonic acidemia with homocystinuria	X				
Malonic acidemia	X				
Isobutyrylglycinuria	X				
2-Methylbutyrylglycinuria	X				
3-Methylglutaconic aciduria	X				
2-Methyl-3-hydroxybutyric aciduria	X				
Short-chain acyl-CoA dehydrogenase deficiency		X			
Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency		X			
Glutaric acidemia type II		X			
Medium-chain ketoacyl-CoA thiolase deficiency		X			
2,4-Dienoyl-CoA reductase deficiency		X			
Carnitine palmitoyltransferase type I deficiency		X			
Carnitine palmitoyltransferase type II deficiency		X			
Carnitine acylcarnitine translocase deficiency		X			
Argininemia			X		
Citrullinemia, type II			X		
Hypermethioninemia			X		
Benign hyperphenylalaninemia			X		
Biopterin defect in cofactor biosynthesis			X		
Biopterin defect in cofactor regeneration			X		
Tyrosinemia, type II			X		
Tyrosinemia, type III			X		
Various other hemoglobinopathies				X	
Galactoepimerase deficiency					X
Galactokinase deficiency					X
T-cell related lymphocyte deficiencies					X

[a]Selection of conditions based on "Newborn screening: toward a uniform screening panel and system." *Genetic Med*. 2006;8(suppl 1): S12-S252, as authored by the American College of Medical Genetics (ACMG) and commissioned by the Health Resources and Services Administration (HRSA).
[b]Disorders that can be detected in the differential diagnosis of a core disorder.
[c]Nomenclature for conditions based on "Naming and counting disorders (conditions) included in newborn screening panels. *Pediatrics*. 2006;117(5 pt 2):S308-S314.

the time, the federal government did not dictate policies on screening but provided guidance. The Health Resources and Services Administration (HRSA) Maternal and Child Health Bureau supported the American College of Medical Genetics to conduct a review of the core NBS conditions. The agency conducted a comprehensive survey on the number of the conditions and the criteria being used to add conditions to the panel. Experts rated the conditions to be either on the primary panel (required) or the secondary panel. The screening criteria were based on Wilson and Jungner (1968), which was considered the gold standard, and had been revisited to address the complexity of and advances associated with NBS.[33] The list was then shared with the SACHDNC, which was made of physicians, parents, experts from medicine, bioethics, and law. Ultimately, the SACHDNC gave approval. The criteria included these questions: (1) Is the condition well-defined? (2) Is there a good screening test available to all? (3) Can the condition be confirmed by

diagnostic testing? (4) Is early treatment available? (5) Does screening do no harm to the baby?[34]

The Evolution of Newborn Screening

In the 1960s, microbiologist and researcher Dr Robert Guthrie developed the first dried blood spot test for phenylketonuria (PKU), historically marking the intersection of clinical medicine, screening systems, public health policy, and citizen-parent advocacy. Guthrie became the international advocate for NBS.[35] Shortly thereafter, approximately 60% of the states had introduced NBS as part of their public health programs, with a number of these mandating screening under public health law. However, the testing algorithms varied, follow-up protocols were not fully developed, and implementation was not uniform across all states. Effective PKU screening was made feasible due to the availability of a low-phenylalanine diet as a treatment[36] and with the support of parents and the medical community. For the past 50+ years, the development of NBS has advanced from bacterial inhibition assays to high-throughput platforms such as sequential multiple analyzers, high-performance liquid chromatography, immunofluorescent assays, tandem mass spectrometry, and, now, next-generation sequencing.[1,2,22,37-39]

The Beginning of the Expansion

From the 1960s to 2000s, there was no uniform federal law that mandated a consensus of diseases to be screened in newborns. During that period, state NBS programs screened between 3 and 10 disorders. In 2005, the committee recommended primary conditions as well as group of secondary targets (see Tables 1 and 2).[29] Today, in 2019, the list of genetic disorders may expand due to the possible application of next-generation sequencing in NBS.

The Present

The NBS program is an integrated system, typically focused on 6 components[40,41]:

1. Sampling and transportation to the testing laboratory
2. Testing laboratory (biochemical and genetic analyses)*
3. Reporting of results, according to predetermined algorithm
4. Follow-up of abnormal results and diagnostic testing through specialist providers
5. Quality assurance and program evaluation
6. Education and outreach to health care providers and advocates

*Screening for hearing and critical congenital heart disease is accomplished at the birthing hospital, with results reported to the NBS program staff.

Screening: A Complex Environment

In the United States, advances in technology and the proactive stance of advocates have driven the expansion of NBS at the state level. NBS began with relatively inexpensive screening for highly treatable conditions and has evolved into a more complex algorithm screening for rarer disorders, a number of which are more difficult to diagnose and treat. Over time, the state screening program has expanded its role in not only screening for more disorders but has also expanded its role in follow-up, diagnosis, and treatment. The National Newborn Screening and Global Resource Center is an important resource for all state programs and advocates.[42]

Expansion of NBS may be opposed by some because of concerns that effective follow-up and treatment may not be available, or that false-positive screening tests may cause more harm than good. Some of these disorders are extremely rare and have later onset forms that may not be detected during the newborn period. Additionally, the natural history for many of these diseases has not been well characterized and effective treatment may not be available. A number of conditions may not lend themselves for inclusion as they may not follow the classic Wilson-Jungner criteria, and as such, require discussion among stakeholder groups and the public health community prior to implementation.[42]

Policy and Finances

Funding and collection of fees for NBS vary by state. There are 2 predominant methods by which state NBS programs are funded: general revenue and fee for service.[43] The executive and legislative branches appropriate funds and determines how the NBS program operates.[44,45] Another option is when state programs offer contractual testing for other states (as in the case of the Massachusetts program, eg, which tests Maine, New Hampshire, Rhode Island, and Vermont newborns) bill each contract state program for specific services, since each state may/may not require testing over and above the 35 mandated conditions.[46] Then there are state programs that have ties with university systems.[44] Each may operate somewhat differently, but scientific support provided by the universities, medical schools, graduate schools, and postdoctoral staff

contribute to effectiveness and innovation. A further example is Illinois, where NBS is structured as a fee-for-service program. Sources of funding such as Medicaid, Children Health Insurance Program, private insurance, and self-pay generally may not affect the program directly.[43,44] Whether or not the hospital receives third-party reimbursement is determined by the hospital.[44] A report published by the Association of Public Health Laboratories contains details about billing practices at public health laboratories.[47]

Determining the Cost of Screening: A Multidimensional Decision Process

In the United States, a baby is screened, regardless of insurance or other third-party coverage. The cost of the screening is covered by a range of avenues such as governmental funds, insurance, and other third-party arrangements.[43] The economic "cost" has not always been a part of the decision-making process in the selection of conditions to be added to the panel.[48] However, the role of cost needs to be considered in decision-making process early on because of the variable treatment cost depending on the genetic disease diagnosed, the hospital billing policy, the infrastructure and personnel cost to run the program, the additional expertise and follow-up systems for surveillance, and treatment for rare conditions, all of which will affect the viability and sustainability of the NBS program.[48,49] Thus, cost is a critical consideration in policymaking.

In order to be cost-effective and cost-efficient, states with fewer births (eg, those with 20 000 or fewer births) may elect to send their samples to a regional screening site.[43] The marginal cost per screening would be lower for states with higher population of births. However, instrument costs for new testing platforms will need to be considered; for example, a DNA-based severe combined immunodeficiency screening platform would cost around $200 000 to $300 000.[50,51] In 2001, the Governmental Accountability Office and the March of Dimes conducted a survey regarding NBS cost of laboratory-based NBS testing, and found the average cost per infants was about $29.44, with 74% of the cost for laboratory testing, while the remaining cost involved covering shipping, administrative cost, and reporting functions.[52] There was a range of cost from $0 to $15 due to testing system or method, instrumentation, staffing, and other actors.[44,53,54] In 2012, Wisconsin conducted an assessment of fees and estimated that in that state, testing cost between $44 and $58, including program administration, but without instrumentation, counseling, treatment, or other services.[44] In other states, the cost of testing was estimated to be $33, while a survey of directors estimated that cost of initial screening was closer to $88, including instrumentation, training, and related costs, which were amortized across the total number of tests performed.[44]

Funding sources may include the following: (1) fees collected from the health care providers, who pass them on to third-party payers and in some case to parents (90% of respondents); (2) federal pass-through sources including Title V Block Grant and HRSA funding (61% of respondents); (3) state general fund appropriation (33% of respondents); and (4) direct Medicaid payment beyond routine newborn care.[44,54]

"Cost" may be understated because of the relative inexpensiveness of adding "just one more test" to an existing screening panel. Costs begin to increase with the necessary acquisition of testing equipment, materials, physical plant, and staff.[54] The cumulative cost of screening is beyond the test cost itself. According to the Hasting reports, a framework for decision-making and policymaking for NBS should (1) be based on evidence, (2) take opportunity cost in account, (3) distribute the cost and benefits of the program fairly, and (4) respect human rights.[30]

Public Health Policy and Practice in Newborn Screening

Multiple facets influence policymaking in NBS, such as the screening test parameters (specificity and sensitivity), cost, reliability, predictive value, the availability, and success of treatment (and early treatment). When the standard of care is uncertain, the variation in public policy will magnify the complexity.[1,48] Setting the standard of health care practice, and thus screening standards, falls within the state authority.[24,55] Some states allow parents to refuse screening based on personal, religious, and cultural reasons.[5,56-59] As the number of the disorders continue to be added, balancing the privacy and rights of parents is important as is debating the uncertainty that screening may produce using tests where the reliability and availability of treatment is limited. Thus, stakeholder involvement and participation in the NBS policy debate is critical in the current time and in future.[60]

New Insights for a Systems Approach for Newborn Screening

The cost of genomic sequencing technologies will continue to decrease, and the speed of returning genomic information for medical management will continue to increase. Thus, we need to consider

capacity building, workforce readiness, and training in public health and medical systems to manage the wealth of information from NBS. Sharing the complexity of genomic information from NBS program to various stakeholders, providers, public health officials, and parents will require knowledge of a systems approach in delivering and maintaining privacy, personal choices, and decision-making. A systems approach for NBS will require the collaborative, collective partnerships from different sectors to support the NBS program enterprise.

Global Perspectives

International meetings focusing on NBS have been held since the 1960s era of screening for PKU. The International Society for Neonatal Screening provides support for the international NBS community such as sponsorship of meetings, provision of guidelines and fact sheets, awards for recognition of contribution to NBS, and other related activities. Six regions have been established to facilitate the sharing of information.[61] Therrell et al[62] provided an overview of NBS in the United States, Canada, Europe, Middle East, North Africa, Latin America, and the Asia-Pacific region. These 6 regions are North America, Latin America, Europe, Asia-Pacific, Middle East, North Africa, and sub-Saharan Africa.

In the international arena, examples of publications since the beginning of 2019 include those offering a 2-tiered test algorithm for spinal muscular atrophy by Strunk et al,[63] approaches to delivery of "Cystic fibrosis screen positive, inconclusive diagnosis" results to parents by Johnson et al,[64] and second-tier testing for lysosomal storage disorders by Burlina et al.[65] These examples from the Netherlands, the United Kingdom, and Italy, respectively, demonstrate the broad interest in and value of research and practice for screening, beyond the historic examples of PKU and congenital hypothyroidism. Technology and stakeholder activities have stimulated interest in expanded screening for Krabbe (and other lysosomal storage disorders), X-linked adrenoleukodystrophy, fragile-X, and other conditions. Legalities, public policy, availability of quality control materials, funding support, and public perception are influencers. Ethical and social issues such as biobanking and long-term storage and use of residual specimens will be part of the discussion and subsequent decision-making. Sharing information from research and pilot studies among international partners is a vital part of the process for expanding NBS, thus increasing the availability of screening and subsequently benefiting wider populations.

Public Health Implications

Moving Forward Future for Decision-Making

Newborn screening expansion should include a rigorous debate for the evaluation of all aspects of the system. The evidence can then be reviewed by those representing different perspectives and with practice expertise in science, medicine, health economic, bioethics, and public health. Opportunity cost and potential benefits beyond the child should be factored in, thus structuring the policy that will fairly distribute cost and benefits. Needed will be transparency in the financing of program, data on the distribution of cost and benefits, and increased uniformity in the access to follow-up and treatment services.[30] This report may be used to explore the role of the policy-making process and different players involved in formulating a consensus of potential benefits before the implementation of new screening technologies.

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KC and MP equally contributed to the development, research, and writing of the manuscript.

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Ethical Approval

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Informed Consent

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