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A Vision of the Future of Newborn Screening

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ABSTRACT

In 40 years, newborn screening has evolved to become a standard component of preventive public health. Despite its widespread acceptance, efforts need to be made to overcome some significant problems. There is inequity in the conditions for which states screen routinely, and many conditions that could be screened for are not, for economic or logistic reasons. Existing (tandem mass spectrometry) and potential (DNA microarray) technologies could be developed and put in place to correct these existing shortcomings. To do so will require investment in the technologies, combined with public and professional education and provision of a high-quality, accessible system for confirmation of diagnoses, family counseling, initiation of treatment, and the opportunity to participate in research to develop new or improved therapies.

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Key Words

newborn screening, recommendations

Abbreviations

NIH—National Institutes of Health

HRSA—Health Resources and Services Administration

MCHB—Maternal and Child Health Bureau

NICHD—National Institute of Child Health and Human Development

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IN ITS >40 years of existence and evolution, newborn screening has changed dramatically. Newborn screening has developed from a program that was viewed with some suspicion by the public to one that is well known and popular. The programs have expanded from using a little-known procedure that detects only 1 disorder to using a widely discussed multiplex procedure that can detect numerous disorders. This new technology has brought broad demand for its consistent use and expansion in newborn screening programs and frustration that it is not used more. With scientific advances providing even newer technologies and the opportunity to respond to those demands for uniformity and expansion, the pediatric and public health communities need to move rapidly to take advantage of the popularity and enthusiasm for newborn screening, to improve the ability to prevent disease and disability in childhood and throughout life.

Four major objectives need to be addressed in the effort to accomplish this task in the immediate future: (1) the inequity among states with respect to the conditions for which screening is performed needs to be eliminated; (2) the number of conditions that are screened for needs to be expanded greatly; (3) the dogma that it is appropriate to screen only for conditions for which effective treatment already exists needs to be changed, by broadening the concept of benefit from screening for the child to include the family; and (4) public and professional education and the expert infrastructure for dealing with children who screen positive need to be improved significantly.

INEQUITY

The difference from one state to another with respect to conditions included in newborn screening programs has increased dramatically in recent years. As documented most recently in a report from the American College of Medical Genetics¹ and described in the article by Therrell et al,² state screening panels vary from 3 conditions to >40. The expansion in conditions screened for has been made possible largely because of the addition of tandem mass spectrometry to newborn screening programs. Even with the expanded capabilities, some conditions for which effective treatments exist are not included in the screening panels of many states. The reasons are varied but often include a conservative stepwise approach to technology implementation or a lack of knowledge about the conditions in question, issues of cost-effectiveness, and the lack of availability of subspecialist diagnostic and treatment services. There are few things in medicine that are more difficult than trying to explain to the parents of a child with brain damage from one of these conditions that, if the child had been born in an adjoining state, he would have been screened and treated for the disorder and would be developing normally. Beyond the will to change, correcting this prob-

lem depends on developing a new screening technology that contains costs by screening for virtually all target conditions with one test system that works at an acceptably reasonable, even cost-effective, level. This test system must be adoptable by every state, so that the diseases for which children are screened do not vary according to the state in which they happen to be born; the current inequity would then disappear. Fortunately, such screening test technology is at hand if the investment is made to develop and to implement it.

EXPANDED TESTING

A number of different approaches to broadening newborn screening beyond tandem mass spectrometry, such as proteomics, microarrays with bead technology and nanotechnology approaches, pulse oximetry, and DNA-based technology, are in various stages of development. DNA chip technology is one development from the Human Genome Project, and some are proposing microarray DNA chip technology as the most advanced method. Currently, the National Institute of Child Health and Human Development (NICHD) proposes to facilitate the development of this technology.

Considering microarray chips as a prototype, the potential exists to screen for any genetic disorder for which the genetic mutations have been identified. The DNA for each gene is placed in a discrete identifiable location on a microarray chip. The chip, which is smaller than a microscope slide, can be made to contain any number of genes up to >25 000 and can be mass produced. To describe this process in its simplest terms, DNA can be extracted from newborn screening dried blood spots (which are collected on filter paper currently) and then sent to a central laboratory. The DNA obtained from dried blood spots is amplified through polymerase chain reaction and exposed to a microarray chip. Automated computer analysis is used to identify any genes in the infant's blood that do not match the normal/normal variant genes on the microarray chip. Children with abnormalities are called back for confirmatory testing to separate false-positive results from true-positive results, just as performed now in existing newborn screening programs. This technology offers the potential, if the genes are available, to screen for many conditions with one test, including genetic metabolic disorders (especially those associated with mental retardation or neurodegenerative diseases), immunodeficiency disorders, muscular dystrophies, cystic fibrosis, hemoglobinopathies, coagulopathies, and genetic deafness syndromes.

With screening directly at the level of the gene, the need to wait for a product to accumulate is eliminated. Screening would begin with genes for conditions for which the genetic mutations are known, which number >100 now, with the addition of genes for more disorders as they become available. Among conditions screened for now, only congenital hypothyroidism, which is

largely nongenetic in etiology, would continue to require a separate test. One significant disadvantage is that the correlation between the genetic mutation and the phenotype is not always well known. A major effort will be required to define genotype-phenotype relationships for use of this approach as the primary approach in newborn screening. As our understanding of the function of the DNA sequences increases, we should see an increase in the accuracy and predictive power of the tests.

This procedure is not necessarily expensive. Theoretically, testing for many conditions at one time on a large (universal) scale of >4 million tests per year and identifying a larger number of preventable or treatable disorders should be cost-effective; however, this will need to be determined in pilot studies.

CHANGING THE DOGMA

With the potential of greatly expanded testing and broader understanding of genetic diseases, many have begun to question one standard tenet of newborn screening, ie, that it is appropriate to screen only for conditions for which an effective treatment already exists. That tenet served a useful purpose in the early years of newborn screening, but it is now being challenged as outmoded because it fails to consider other benefits of diagnosis in the newborn period and dooms us to continued ignorance and unavailability of treatment because affected individuals are not identified until they exhibit symptoms, too late for effective preventive interventions to be tested or applied.

Arguments for considering broader benefits from the early diagnosis that only newborn screening can provide include benefits to the child and family such as avoidance of years of looking for a diagnosis after symptoms begin; knowledge on which to base reproductive decision-making years before a disease would be diagnosed for the affected child; benefits of adjunctive, if not curative, therapy and early intervention programs for the child; and the potential for the child to participate in research on innovative therapies intended to prevent or to modify manifestations of the genetic disease. These innovative therapies would be facilitated by parents being offered the possibility of listing the child in a registry of persons affected by the disorder, with protection of privacy and confidentiality; agreeing to be contacted when investigators are proposing new experimental interventions for the disorder; and, after being informed, deciding whether to enroll the child in the study. There is hope of developing and evaluating effective therapies only with early presymptomatic identification of the disorder and the availability of sufficient numbers of presymptomatic patients with rare disorders that a registry can provide. The old dogma cannot be allowed to stand in the way of developing effective treatments for these rare genetic disorders.

EDUCATION AND INFRASTRUCTURE

Expansion of newborn screening as a stand-alone test will create problems unless it is accompanied by major efforts to educate and to prepare health care professionals and the public, as well as to provide the necessary accompanying infrastructure to evaluate and to treat children who screen positive. Expectant and new parents need to know that they will be informed before their newborn is screened, what screening involves, what the follow-up process will be, and that they will be asked to give their permission, at least for screening for the conditions for which there is not yet an effective treatment. The added complexity of this informing/educating process will require additional training of personnel. Practicing physicians, nurses, counselors, and other health care providers will need to understand the system well enough to explain it to parents and to answer their questions. Special preparation will be required to deal with questions and referrals for any child who screens positive, including reassurance that a positive screen is not a positive diagnosis until it is confirmed and most infants will turn out not to have the disorder, although it is absolutely necessary to follow through with the confirmation process. State health department laboratories or private commercial laboratories will need new equipment, trained personnel, quality control procedures, and follow-up notification and tracking procedures for transmitting and receiving results. A system of state or regional organizations, such as the Health Resources and Services Administration (HRSA)/Maternal and Child Health Bureau (MCHB)-funded Regional Newborn Screening and Genetics Collaboratives, working with referral centers of excellence is needed to coordinate the follow-up evaluation (with definitive diagnostic tests) of infants who screen positive, to communicate and to coordinate with medical providers, to counsel parents, and to initiate treatment and follow-up monitoring. A registry with privacy protections needs to be established to offer possibilities for participation in trials of new therapies to families with affected children. Only if this entire infrastructure is in place and working well can a system that involves the sensitive issue of genetic screening and testing earn and maintain the confidence of the public, allowing its enormous benefits to be achieved.

THE VISION AND ITS IMPLEMENTATION

The successful expansion of newborn screening depends in part on developing laboratory capacity systems that are reliable, accurate, cost-effective, and timely, that can achieve high throughput, and that embrace scientifically sound technologies. Establishing these systems in an effective way that maintains public support and serves children and families requires a planned, concerted, long-term effort. It will not happen without the leadership of the federal government, in partnership with medical care providers, state health departments, advo-

cacy groups, and industry. The first steps are underway; with advice and guidance from the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, the entire system could be in place and operating within a decade.

The recent past, exemplified by the development of newborn screening for phenylketonuria and sickle cell anemia, shows that the federal government has had a partnership with states and the private sector to ensure the strength of newborn screening programs. The federal newborn screening activities described by Lloyd-Puryear et al³ demonstrate the continued need for federal-state partnerships to ensure the success of newborn screening programs. The examples illustrate the commitment by the federal government to support and to facilitate the appropriate introduction of newborn genetic testing into clinical and public health practice. Federal funding has been the impetus for research, development of policies and guidelines, implementation, quality assessment, and program improvement. Federal monies have also been used effectively for developing educational materials; supporting training and educational activities; and facilitating discussion, communication, and dissemination of critical relevant findings. Frequently, initial funding for various demonstration program activities has led to supplemental funding of more-comprehensive program implementation.

To ensure equitable public health prevention activities across the country, it is likely that the federal government will be asked to provide additional support, as well as prudent exercising of responsibility and leadership. Because of the perception of unfunded mandates being issued or because a state may not have the capacity to respond to a federal recommendation, tension may arise with federal efforts to achieve equity. It remains to be seen whether the federal efforts will be supported and will be sufficiently responsive and adequately financed to ensure public health oversight of newborn screening programs while encouraging innovation in the use of technology.

Although the National Institutes of Health (NIH) has supported most basic scientific research projects, the HRSA, the Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality have supported projects related to secondary data analysis, information development and dissemination, education and training, implementation, and postdevelopment issues. The bulk of research implementation efforts for newborn screening programs and other relevant translational activities continue to be provided by MCHB.

The NICHD is focusing on expanding screening technologies and developing effective therapies as concomitant activities. Efforts to develop effective treatments must be the first step. This first step will be accomplished through a program announcement issued by the NICHD

that urges scientists to develop and to submit to the NIH for possible funding new research proposals to develop and to test innovative therapies for genetic conditions that now have no effective preventive therapy, with the goal of testing the therapies among presymptomatic infants identified from the registry. The second step is a solicitation requesting proposals for funding from industry or other groups to apply new technologies, such as microarray chips, to newborn screening. Once prototypes of these approaches are developed, funding will be provided to pilot test them in collaboration with state newborn screening programs that have the requisite referral centers for confirmation of diagnosis, counseling, and follow-up care.

These centers could improve the process of adding new testing technologies, improve screening methods for existing technology, establish capacity for long-term assessment of health outcomes and treatment efficacy and for general program evaluation, and serve as centers for training and education. Initially, these program testing sites would be those that can already provide the infrastructure for confirming diagnoses and making follow-up arrangements; they would need to add the training and education components. Development and testing of the registry would also begin at this time. Cost analysis data would be collected to provide an indication of cost-effectiveness, to guide scale up to broader (nationwide, it is hoped) application with the same system and same disorders screened for in every state. A collaborative effort with the infrastructure of the MCHB Regional Newborn Screening and Genetics Collaboratives and the rare disease centers of excellence funded by the NIH, Office of Rare Diseases, could be envisioned.

The technology could be expanded to screen for additional disorders as mutational analysis or other multiplex technology become available, with decisions being based more on what not to screen for (perhaps Huntington disease) than on what to include. Advice from a national Advisory Committee on Newborn Screening Practices, comparable to the current Advisory Committee on Immunization Practice, could be useful in these decisions. All of this will require major coordination efforts between federal agencies (NIH, HRSA, Centers for Disease Control and Prevention, and Agency for Healthcare Research and Quality), state health departments, professional organizations (American Academy of Pediatrics, American Academy of Family Physicians, and American College of Medical Genetics), and advocacy groups (March of Dimes, National Organization for Rare Disorders, and many others). The overall guidance and advice from the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children will be essential as these programs develop. Support from the public for the implementation and maintenance costs for this extensive system will be required at the federal and state levels, to incorporate into the public

health system a new and highly effective tool for preventing disease and disability for the benefit of all of our children.

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