Newborn screening (NBS) programs are an anomaly in medicine—a universally applied, state-mandated evaluation of healthy individuals. The program had its origin in the presymptomatic diagnosis of phenylketonuria (1), but as technologies for the use of dried blood spots (DBS) have improved, there has been a rapid expansion of the number of disorders evaluated, as well as an increase in the governmental mandates for testing (2).

DNA-based diagnosis is already a feature of NBS. The first integrated use of genetic testing was for the confirmation of hemoglobinopathies (3). Genetic testing is now used as a primary or confirmatory technique in nearly every NBS system in the US. In addition to the analysis of sequence, DNA-based testing can also be used to detect the normal maturation of cell-mediated immunity through the detection of T-cell receptor excision circles (TRECs) (4). Clearly, additional tests will be added over time. The expanded use of DNA-based testing in NBS requires a reliable extraction method that delivers genomic DNA of sufficient quality and quantity for downstream applications.

Improving DNA Extraction from DBS

In this issue of Clinical Chemistry, Saavedra-Matiz and colleagues report details of the DNA-extraction protocol used in the New York State Newborn Screening Program (5). The source of the DNA sample is DBS on 903 filter papers, which are commonly used in NBS. Therefore, changes in the collection technique (i.e., phlebotomy), the volume of blood collected, or the type of card used for collection would not be required for most screening programs. The key advantages of this protocol are its extremely low cost and simplified use of automation. The minimization of hands-on work reduces labor costs and the chances for the introduction of error. The authors’ system is easily scalable to the number of samples that might be reasonably anticipated in a state screening system that uses simple pipetting robots and other commonly available equipment.

The authors demonstrate the quality and yield of genomic DNA by several downstream applications. They include conventional sequencing after multiplex PCR and the evaluation of TRECs. Worth noting is that the authors use this method to provide DNA for several tests currently in use in the New York State Newborn Screening Program, which can evaluate >1000 samples daily. They also report the successful use of recovered DNA in genomewide analysis of single-nucleotide polymorphisms and massively parallel sequencing (MPS) of a small number of genes. These latter techniques are not yet used widely in the NBS arena, but they have been considered (6) and will clearly be in use shortly.

The only shortcomings to this study are the lack of relevant comparisons. Commercial protocols exist for the isolation of genomic DNA from DBS, but the expense of these protocols may be higher. Simplified protocols that use noncommercial reagents have been reported (7), and it would have been interesting to evaluate the differences between methods in performance. The method the authors have reported is effective and inexpensive, and the short duration of the protocol suits the needs of an NBS laboratory. The importance of this work is that it provides a stable platform on which to build new DNA-based testing into existing screening programs at low cost.

The Future of Genetic Testing in NBS

The NIH recently issued a request for applications for studies into the use of MPS of the whole exome or whole genome in the context of the newborn screen. This forward-looking request invited considerations of the coverage of additional metabolic disorders for which treatment might be available but blood analyte analysis is impractical because of poor sensitivity or specificity. It also sets the stage for substantial expansion of NBS, with the potential to detect disorders that have never been under the purview of NBS programs. Although Saavedra-Matiz and colleagues did not examine the ability of their DNA to be used for amplification after whole-exome capture, their work shows a way forward to a time when we could conceivably have exome- or genome-level sequence analysis of all newborns.
The promise of genome- or exome-level sequencing in NBS is too great to ignore, but this promise will be balanced by unique challenges. It is interesting that the American College of Medical Genetics wrote a position paper in the last year that opposed, at least at present, the use of MPS as a primary screening tool. The advantages of a whole-exome approach to NBS include the ability to evaluate health risks comprehensively, prevent morbidity and mortality from inherited disease, and reduce costs to the healthcare system by preventing both symptoms of disease and recurrence. An expansion of NBS to this level for the 4 million children born annually in the US is an enormous technical challenge and would have high up-front costs, but the technological and financial challenges will diminish with time. By contrast, the legal and ethical perils will remain.

The Legal Basis of DNA Testing in NBS

Genetic testing within the newborn screen occupies an unusual legal niche. The NBS program, as constituted in all states, is an opt-out program. For example, parents wishing to decline in New York must be a member of a recognized religious organization whose teachings object to the testing requirement, and parents must also sign a waiver agreeing to the consequences of refusing testing. This is a reversal from the normal approaches to genetic testing, in which patients or their guardians must opt in, be informed of their rights, and often sign a release to engage in testing.

In the US, the performance of NBS, inclusive of genetic testing, is guaranteed by statute in each state. Legal challenges to these laws have generally failed, e.g., Spiering v Heineman, in which the United States District Court refused to force a religious exemption into Nebraska state law. There has been a recent spate of cases, however, in which the right of states to use residual NBS cards for population DNA research has been considered. In these cases, the state laboratories have frequently lost and/or had to destroy NBS cards; other states have passed laws either preventing studies of residual DNA on NBS cards or mandating the creation of opt-out systems for parents.

The expansion of NBS to the levels of the genome and exome would certainly involve additional legal challenges. The public has a level of awareness of the rights of genetic privacy, and these rights are enshrined in such laws as the federal Genetic Information and Nondiscrimination Act, which bars discrimination in employment or insurance decisions on the basis of genetic information. There is also a level of public resistance to governmental agencies having access to this information. Such attitudes perhaps originate from dystopian films and literature that envision a future of state-supervised genetic determinism.

Medical Ethics and Genome-Level Sequencing

Beyond the legal problems that would be encountered upon the introduction of MPS to NBS, it is unclear what information can and should be communicated to the families of newborns. The use of MPS in the clinical diagnosis of patients in complex cases has already shown that it may reveal unexpected and even unsettling results that do not relate to the phenotype under study. Hierarchies for evaluating the importance of results and for the reporting of important and incidental results have been recommended, but it is difficult to create guidelines that respond sensibly in all circumstances.

Performing whole-exome or whole-genome studies in the context of NBS is potentially more troublesome, because in some sense all findings are both relevant and incidental in a healthy newborn. A frequent ethical puzzle in genetics is whether one should return a result indicating the risk for an incurable neurodegenerative disorder in an asymptomatic patient if the risk for this disease was not the indication for testing. A survey of geneticists found that few would communicate an incidentally detected risk for Huntington disease or Alzheimer disease to patients who have undergone whole-exome sequencing. This problem is compounded when testing is performed in the context of NBS. It would be very difficult to cast such a shadow over a family, yet the failure to disclose this information makes the questionable assumption that these disorders will not be treatable during the life span of someone who has just been born.

In conclusion, the technologies for expanding genetic testing in the context of NBS are at hand. The challenge is to perform these screens effectively and to the fullest benefit of our patients.

References


