Quality improvement of newborn screening in real time

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It is exciting to read the clinical research article in this issue of *Genetics in Medicine* by McHugh et al.[1] The article is based on a clever, innovative, and original idea. In clinical medicine, we usually define "normal" based purely on a statistical analysis that defines normal and abnormal. To accomplish this, one collects a sizable number of samples, such as blood, from a "normal" population and, after measuring the analyte of interest, we decide that the top and bottom 5% of the values obtained are indeed "abnormal." In most situations, a single laboratory can generate sufficient data to independently refine its own performance. However, as nearly all conditions identified in newborn screening (NBS) are rare or ultra rare, obviously one would have to have samples from a very large number of affected infants and their initial tandem mass spectroscopy (MS/MS) values to establish appropriate cutoff target ranges. But to accomplish this effort, you would indeed need data from literally millions of newborn infants. McHugh et al.[1] felt it would be much more informative for NBS to have actual NBS values from dried blood spots from infants who were in time confirmed to have the disease of interest. Their work focused on those conditions identified by MS/MS, which covers most conditions on the "core" panel. In this fashion, you would have actual evidence-based values from affected infants for comparison with the normal newborn population.

The need to capture as much data as possible from affected infants led to another remarkable aspect of this publication, i.e., the vast number and distribution of the experts who contributed the data. This began with the Mayo Clinic group carrying this out as a part of their Region 4 Collaborative project, a part of the US Regional Genetics and Newborn Screening Services Collaboratives priority projects. These important projects are funded by the Health Resources and Services Administration covering every region of the United States and are planned to encourage cooperative efforts in the various regions (geographically). The coordinating center for these Regional Collaboratives is operated by the American College of Medical Genetics under a cooperative agreement with Health Resources and Services Administration. The Mayo group invited NBS groups from around the United States, and later indeed the entire world, to contribute data to this project. It is stunning that the current coauthors number more than 200 persons from virtually every part of the world, including more than 35 countries. This group had screened more than 30 million newborn samples to provide 10,679 samples from affected infants! One has to examine literally millions of newborn infants to have even a handful of true positives for some of the very rare conditions. These numbers are truly staggering.

Why in the world would so many experts in the NBS community bother to provide data to this project and what benefit is derived by those providing data? First, a very user-friendly on-line data system was designed. But most importantly, each person participating could examine the combined worldwide data for each of the MS/MS analytes from literally millions of dried blood spot samples from all of the other laboratories. There was rigid security that allowed one to see the data from the various laboratories but did not permit any user to see the identity of participating laboratories other than their own, thereby allowing them to see their performance compared with the other participating laboratories. The system is "live" and is updated regularly when new data are entered. It has been invaluable for the individual participant who could immediately see how well they were doing, i.e., what was the clinical sensitivity and positive predictive value in their laboratory. Some laboratories had defined cutoffs that resulted in high predictive values, whereas others lagged. This was a very powerful incentive for laboratories to work on their cutoff ranges to ensure that very few, if any, babies with disease were missed, but at the same time they would have cutoff values that reduced the false-positive rates. There has been a clear-cut improvement in the positive predictive values for some of the laboratories using this site. I am sure this will continue.

In NBS, we have long been concerned about false-positive rates. Such false positives create considerable anxiety in parents as well as the physicians and others. A follow-up on false-positive tests dramatically expands the work and cost of the laboratory and the NBS program and that of the laboratories and physicians who provide the diagnostic follow-up of those identified by the screening program. By refining the cutoff target ranges in NBS, and thereby increasing the positive predictive values, false-positive tests can be dramatically reduced. This is a vital product of this effort.

In addition to having the ability to dramatically improve the performance of the individual laboratory and refine the positive predictive value of the individual test, this methodology and program will have a great value going forth in the prospective performance of necessary pilot studies in NBS. Before national adoption of NBS for a new condition, it is essential to have excellent data before "going live" nationally. By combining and monitoring values in various laboratories involved in the pilot studies, the cutoff values can be more accurately defined and the impact of confounding variables such as prematurity or concomitant conditions can be assessed more robustly.

This remarkable study not only represents creative thought about establishing evidence-based values for NBS but also demonstrates the value of the largest international study ever conceived and performed in NBS. Such vast sample sizes will be required to refine the cutoff target ranges in NBS due to the individual rarity of the diseases as we move forward with expanding and improving our NBS programs.

Not only does this article represent a powerful model for dealing with rare diseases in the context of NBS, its implications extend beyond the NBS world. For example, the broad genomic community could benefit by adapting this type of organized worldwide approach, as it seeks to define the significance of the rare variants that are being discovered as whole genome sequencing is widely implemented.

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1. McHugh DMS, Cameron CA, Abdenur JE, et al. Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide collaborative project. *Genet Med* 2011;13:230–254.