COMMENT | Genetics inMedicine

We must now put in place an updated, comprehensive newborn screening program for deaf and hard-of-hearing infants

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More than 15 years ago, a large and distinguished panel was convened by the American College of Medical Genetics and Genomics (ACMG) to fulfill a contract it had received from the US Department of Health and Human Services. This group of physicians, laboratorians, geneticists, ethicists, lawyers, and families was charged with developing a plan to bring order, rationale, and credibility to the lifesaving newborn screening program in the United States. The newborn screening system was in considerable disarray at that time. Since the extremely successful newborn screening program for phenylketonuria was launched in 1960, additional conditions had been added to the newborn screening panels, state by state and without careful attention to the rationale for selection. Because newborn screening programs are all under the direction of state health departments, the programs varied enormously not only by the number of conditions screened, but also by what conditions had been selected for individual programs. The ACMG group reviewed conditions that had been screened for in the newborn period in any organized program. The group then used modified Wilson–Jungner criteria, updating and expanding them to consider the screening test, the treatment, natural history of the disease, clinical significance, available treatment, and benefit to the infant and the family. Based on these and other factors, conditions being considered for the panel were assigned a number, quantitating the criteria used for recommending screening. These conditions were then ranked, and those with evidence bases to support a high score were categorized as conditions to include in a recommended uniform panel. The recommendations of this group were finalized and later published in 2006 as a supplement to *Genetics in Medicine*.[1] These recommendations were soon reviewed by the newly established, congressionally mandated Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, which accepted this report and recommended it to the Secretary of Health and Human Services. The importance of this recommendation from a federal advisory committee was promptly recognized by its coverage on the front and continuing pages of *The New York Times*. Soon thereafter, the Secretary of Health and Human Services approved this recommendation, and declared that implementing this recommended uniform panel was now the standard of practice in the United States.

The very first Recommended Uniform Screening Panel (or RUSP) from the American College of Medical Genetics group included newborn screening for hearing loss.[1] This was also the very first point-of-care newborn screening test that was recommended for the RUSP. Newborn screening for hearing loss had been going on for some time in many states, and had developed outside the ongoing newborn screening programs, which were focused on metabolic disorders. These existing newborn screening programs utilized dried blood spots that were sent to and analyzed by either state health department laboratories or commercial laboratories contracted by the states. It is interesting, and important, to note that the experts who reviewed the evidence considered by the group working under the ACMG contract to devise the original RUSP were recognized experts Cynthia C. Morton and Richard J. Smith, authors in the two important contemporary papers cited by this commentary.

Newborn screening has long been driven by technology, particularly as newborn screening has greatly expanded in regard to the diseases being screened, as well as the methods used for this screening. The original group that worked on the recommended uniform panel expected that there would be developments in the diagnostic tests and treatments for these rare genetic conditions that were already on the panel, and that other serious, treatable conditions would be considered for addition to the panel as tests and/or treatments were developed. One of the early changes involved the laboratory test used in newborn screening for a condition already on the RUSP, i.e., tyrosinemia type I. It was recognized early that the tyrosine content on the dried blood spot, which was the analyte used in newborn screening, was not a reliable

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predictor of tyrosinemia. Now, the analyte used to screen for this condition has shifted to succynl acetone. It is therefore not only appropriate, but expected, that screening for important disorders, such as those leading to deafness and hard of hearing, will be modified and expanded as our information grows, as we identify more infants and a greater spectrum of causes and possible treatments for the conditions for which newborn screening is undertaken.

When the recommended uniform panel was first established, 42 states were already screening newborn infants for hearing loss. This had begun as there was widespread recognition that the early identification of newborns who are deaf or hard of hearing would permit early intervention and thereby markedly improve outcomes in many areas. It was known that there were ethnic differences in incidence and distribution of deafness. The genetic details underlying deafness were yet to be characterized. The available technology for newborn screening at that time was solely physiologic. Cytomegalovirus infections in infancy were known to cause deafness, but no system to diagnose and treat such infants existed. Over the following decades, an enormous amount has been learned about the genetics of deafness as well as the importance of congenital cytomegalovirus (cCMV) as a major cause of childhood hearing loss that might indeed be treatable. We have learned that our current physiologic testing misses some infants with deafness. The large number of infants who fail current screening tests and who are lost to follow-up has been a major problem, and remains at an unacceptably high level. The point-of-care testing for deafness had developed outside the traditional newborn screening program, and this probably contributes significantly to the serious issues surrounding follow-up that continue today. Newborn screening tests carried out by state laboratories (on dried blood spots) include a very effective follow-up program such that virtually all abnormal tests are followed up. In spite of these recognized issues with the current screening program, virtually all the babies born in the United States are currently screened for hearing loss, and the program is invaluable. However, since we miss infants with our current screening technologies, we do not routinely provide etiologic information, we must reduce the numbers of infants lost to follow-up, and we must devise appropriate programs to diagnose cytomegalovirus in the newborn period, and treat those infants so diagnosed.

Clear studies have shown that adding population genetic screening improves the outcomes for infants at risk for hearing difficulties. In a recent study published in this journal[2] 1,172,234 newborn infants in China were subjected to concurrent newborn physiologic hearing screening, along with newborn genetic screening using the traditional dried blood spot for analysis. Limited genetic screening entailed genotyping 20 genetic variants associated with deafness in their population. This Chinese study identified 107 infants with hearing loss at follow-up. Of those infants 95 were identified by physiologic screening, but 12 infants were identified solely based on genetic screening results. Although false positive results in newborn screening tests create significant problems, missing infants who are affected by the condition(s) for which screening is undertaken is simply not acceptable.

The Chinese scientists—working with BGI, the world's largest genome sequencing facility, located in Shenzhen, China—were able to provide the genetic results rapidly, usually within 2–4 weeks. In addition to identifying the infants with specific genetic defects producing hard of hearing, an additional benefit of the genetic testing was that the scientists were able to provide information about the infants who were *MT-RNR1* variant carriers, and who were at risk for hearing damage when exposed to aminoglycoside drugs. In the infants studied, 2638 (0.23%) newborns were shown to be predisposed to ototoxicity that would not have been detectable by traditional hearing screening. Such information will permit these individuals to avoid aminoglycoside drugs and therefore hearing loss.

The critical paper from the Newborn Hearing Screening Working Group[3] published in this journal outlines the key issues that have been learned from decades of newborn screening for deafness and the current state of information about deafness, including the enormous genetics discoveries that have been made. The authors provide an outstanding proposal that will address contemporary needs for newborn screening for deafness. These issues include the need for genetic diagnoses, approaches for cytomegalovirus testing, the unacceptable numbers of infants lost to follow-up, and the very low positive predictive value of current physiologic testing alone. It is my opinion that working more closely with the mandated state newborn screening programs will be particularly helpful in dealing with the lost-to-follow-up issues.

The need to include comprehensive genetic testing is well documented in newborn hearing screening, and the recommendation of this group to identify the optimal method, both with regard to value and cost, of population wide genetic screening will require substantial research study to finalize.

Similarly, the leading nongenetic cause of deafness at birth is cCMV infection, recognized to cause 10–20% of congenital and childhood deafness. These CMV infections present the promise of benefit from treatment. Critical research efforts must be launched to define the most effective, and practical, method of detecting CMV infections in the entire newborn population.

The current, effective newborn hearing screening program using physiologic technology has benefited hundreds of infants with deafness, and provided them with life-altering treatments and benefits. This program has been, and remains, invaluable. Based on the experience gained with this effort over recent decades, it is now time to focus on, and correct, the deficits that have been recognized. Studies have clearly indicated that the time is here to integrate genetic screening as well cCMV screening (and treatment as necessary) into our current physiologic testing program. Before this can move forward, it is urgent to enhance and fund research efforts in these areas to identify best practices in implementing them in a broad, public health fashion.

Every deaf and hard-of-hearing infant born in our country deserves to be accurately identified at birth, and provided with

proper, early, life-altering treatment. We must provide the technologies and plans to accomplish this. Nothing less is acceptable.

DISCLOSURE

R.R.H. declares no conflicts of interest.

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