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PERSPECTIVE

Newborn Screening: Adapting to Advancements in Whole-Genome Sequencing

Caroline Meade[1,2] and Natasha F. Bonhomme[1]

September is newborn screening awareness month. Since 1963, state public health programs have screened newborns for a number of life-altering health conditions. Many of these disorders are rare and genetic, and if caught in the first weeks of life they can be treated or managed to prevent death or a lifetime of disability. Early detection can also help families avoid the lengthy and stressful ''diagnostic odyssey'' involved in finding out what ails their child (Exe *et al.*). In 2013, the United States celebrated the 50th anniversary of newborn screening. From scientist Robert Guthrie's discovery of a test for phenylketonuria to development of state programs that screen every newborn for up to 56 conditions, newborn screening has saved and improved millions of lives. State-mandated screening gives newborns their best chance for typical development, in large part because of strong national guidelines and efficient state public health systems that have been evolving to support screening for the last 50 years.

As newborn screening success stories gained national notoriety in the early 1960s, scientists quickly discovered diagnostic tests for a host of genetic disorders that could be treated at birth. State public health officials then responded by developing mandatory screening programs with inclusion of increasing numbers of genetic and metabolic conditions. While testing every newborn at birth is a seemingly simple process, organizing the resources required for obtaining samples, analyzing results, diagnosing disorders, and providing follow-up care is a large undertaking for state public health systems.

Since its inception, the newborn screening program has seen continued improvement. Creation of the International Society for Neonatal Screening in 1988 and the signing of the Newborn Screening Saves Lives Act of 2008 are examples of initiatives to increase education and funding for newborn screening in an effort to adapt to new discoveries and methods for treating rare or genetic diseases. Recently, the cost of whole-genome and whole-exome sequencing has decreased dramatically, emphasizing the potential for genome sequencing to affect newborn screening programs. Newborn screening policymakers and stakeholders must respond to these advancements as they have responded to others in the past, recognizing that while some technological updates have a place in the newborn screening system, others may not. As public health officials work to come to a conclusion on whole-genome sequencing for newborns, it is important to keep the interests of families and children at the forefront of the discussion.

In June 2014, a geneticist sequenced his son's genome at birth, making the child one of just a few thousand healthy newborns in the United States who have undergone this type of testing (Regalado, 2014). Inova Translational Research Institute is also offering newborn genome sequencing as a part of their Childhood Longitudinal Cohort Study, which looks to learn about disease by tracking 2500 children in Fairfax County, Virginia, from pregnancy to age 2 years (Inova Translational Medical Institute, 2014). The press surrounding both the father's controversial decision and Inova's study highlights the evolving debate over whether whole-genome or -exome sequencing for healthy newborns has a place in public health screening programs. Currently in newborn screening programs across the country, whole-genome sequencing is used only as a secondary method to confirm positive test results for genetic disorders such as cystic fibrosis or sickle cell disease, but experts have suggested that in the next decade large-scale sequencing for all healthy babies at birth could be plausible (Knoppers *et al.*, 2014). As of this writing, the American College of Medical Genetics and Genomics had not yet released an official position on genome sequencing for newborns, although they have presented preliminary guidelines for genome sequencing and its clinical application in adults and children.

It is important when discussing potential updates to newborn screening programs to keep the typical parent with minimal genetic testing experience in mind. Goldenberg and colleagues did just this in 2014, surveying parent opinion of whole-genome sequencing for newborns if it were offered by newborn screening programs or pediatrician services. In both scenarios, about 70% of parents expressed interest in whole-genome sequencing, citing test accuracy and the ability to protect a child from developing a disease as important factors in their decision-making process (Goldenberg *et al.*, 2014). In addition to confirming preliminary parent interest in whole-genome sequencing, research has determined that genome sequencing may be less costly and faster than conventional newborn screening processes, with the ability to produce results in 50 hours rather than the typical

[1]Genetic Alliance, Washington, District of Columbia.
[2]Duke University, Durham, North Carolina.

4–6 weeks (Saunders *et al.*, 2012). Lower cost and shorter time to results could be beneficial in lessening public health costs and parent anxiety; however, the possibility of learning a child's susceptibility to more than 3000 diseases, some adult-onset and some without cures, presents a daunting ethical and public health concern to policymakers.

While genome sequencing has the potential to detect disease and improve health outcomes, an assessment of its impact on individuals, families, and overall health is needed before public health programs could ever implement official clinical whole-genome sequencing for newborns. Responding to this need for large-scale evaluation of newborn genome and exome sequencing, the National Institutes of Health awarded $25 million over 5 years under the Genomic Sequencing and Newborn Screening Disorders program to four grantees, with the goal of exploring the use of genomic sequencing in newborn healthcare, in the fall of 2013 (National Institutes of Health, 2013). The grantees for 2013 are implementing studies to explore best practices for delivering sequencing results to parents, as well as looking at the law, policy, and ethics of newborn exome and genome sequencing. Outcomes of these earliest large-scale assessments of the risks and benefits of genome sequencing for newborns will help to inform newborn screening policy for the future, but today the topic of newborn genome sequencing as a public health initiative remains contentious.

Is whole-genome sequencing of newborns best left to the private sector of health? Newborn screening is a highly successful public health program, and addition of whole-genome sequencing would require a complete overhaul of a system that has saved millions of lives. Private-sector whole-genome sequencing at birth instead puts the ethical and financial burden of interpreting results primarily on new parents, private practice genetic counselors, and nongovernment labs. Before whole-genome sequencing could ever be of value to newborn screening programs and families, public health initiatives would need to create an infrastructure that could properly support whole-genome sequencing outcomes. It may also be prudent while considering whole-genome sequencing of newborns to simultaneously improve prenatal screening and carrier testing protocols. Although generally not included in public health–based screening, prenatal testing for genetic disorders gives parents who choose any of the many tests available ample time to consider their options and prepare for a child who could be born with health challenges. Carrier screening identifies the likelihood of offspring having a genetic disorder before conception and during the prenatal period. For both, the ethical implications and clinical outcomes are more clearly defined than those for whole-genome sequencing. Increased public health initiatives for prenatal testing and carrier screening have the potential to drastically reduce the incidence of infants born with genetic disorders and also better prepare parents for the outcomes of their pregnancies.

Regardless of where newborn whole-genome sequencing ends up within the health sector, policymakers need to tackle challenges, such as storing vast amounts of sequence data securely, developing genetic counseling techniques to advise new parents, and establishing ethical standards for the practice as a whole. These challenges also apply to prenatal and carrier testing initiatives. The public health community must decide whether the benefits of adding whole-genome sequencing to well-established newborn screening programs outweigh the associated ethical pitfalls, while also preparing to educate families about the option of whole-genome sequencing for their newborn.

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Address correspondence to:
Sharon F. Terry, MA
President & CEO
Genetic Alliance
4301 Connecticut Avenue, NW
Suite 404
Washington, DC 20008

E-mail: sterry@geneticalliance.org