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What Genomic Sequencing Can Offer Universal Newborn Screening Programs

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Massively parallel sequencing, also known as next-generation sequencing, has the potential to significantly improve newborn screening programs in the United States and around the world. Compared to genetic tests whose use is well established, sequencing allows for the analysis of large amounts of DNA, providing more comprehensive and rapid results at a lower cost. It is already being used in limited ways by some public health newborn screening laboratories in the United States and other countries—and it is under study for broader and more widespread use, including as a core part of newborn screening programs.[1] Sequencing technology has the potential to significantly improve these essential public health programs. For many of the conditions that newborns are already screened for, sequencing can return more specific and more sensitive results. The technology could also enable newborn screening programs to expand the list of rare pediatric conditions that they look for, thereby identifying more infants who can benefit from immediate care.

In some U.S. states, sequencing is already used as a follow-up test in newborns who have screened positive for certain conditions on initial or first-tier newborn screening tests. For conditions like cystic fibrosis[2] and lysosomal storage disorders,[3] sequencing can help to confirm a diagnosis and can provide additional prognostic information.[4] For nonspecific disorders, such as immunodeficiencies and hearing loss, gene panels or whole-exome sequencing can help determine the underlying cause of the condition, information that is critical for appropriate medical management, surveillance, and treatment.[5] In the future, widespread use of sequencing as a diagnostic follow-up to existing screening tests could also decrease the number of false positives generated in public health programs, thereby lessening the emotional and financial burden on parents and the health care system. As one example, elevated phenylalanine levels detected using today's main newborn screening technology (tandem mass spectrometry) are associated with phenylketonuria (PKU) disease, the disorder that drove the establishment of newborn screening programs worldwide. But these same elevated levels can also indicate what is known as benign hyperphenylalaninemia, which requires no intervention or treatment. Sequencing the gene associated with PKU could, in the future, help clinicians and parents distinguish the two, thereby avoiding unnecessary treatment[6] and, for an infant who does have the disease, predicting the effectiveness of treatment.[7]

Genome sequencing also has the potential to become a primary test in newborn screening programs. It would enable public health programs to look for conditions that meet the criteria for newborn screening but that are not currently screened for because there is as yet no way to detect these conditions. These conditions include certain childhood cancers and cardiac arrhythmias.[8] Expansion of screening programs in this way has the potential to save

and improve lives of infants around the world. Use of sequencing in these programs could also benefit families. Molecular confirmation of a disorder in an infant can suggest the need for testing of other family members (known as “cascade testing”) and can inform parents’ decisions about use of in vitro fertilization with preimplantation genetic diagnosis or prenatal testing in future pregnancies.

Including sequencing in state newborn screening programs would ensure that the benefits of sequencing can be provided to all infants because the cost of this testing would be covered by state departments of public health. If that same testing were done in the context of the infant’s pediatric care, state Medicaid programs or third-party payers would be billed, and they might not cover genetic testing. Medicaid coverage for genetic testing varies greatly between states, with some having liberal coverage for indication-based testing and others denying all molecular genetic testing. Coverage by insurance companies also varies, depending on the individual’s policy and the company. Including sequencing as part of the newborn screening program will prevent the scenario in which infants without coverage are denied confirmatory genetic testing.

Although the cost of sequencing has not yet dropped to levels that make its universal use feasible for public health programs, further cost reductions are likely, and the day may soon come when public health programs can afford to sequence every baby’s genome. When this happens, programs will likely opt to perform whole-exome sequencing followed by targeted analysis rather than using targeted gene panels. While use of next-generation sequencing with targeted gene panels avoids the dilemma of sequencing genes associated with disorders for which newborn screening is not intended, gene panels have to be updated and revalidated each time a new gene is discovered, requiring additional time and cost. Use of whole-exome sequencing followed by targeted analysis avoids this problem. Newly discovered genes can quickly be added to those analyzed at minimal to no cost by updating the informatics that guide analysis. Whole-exome or whole-genome sequencing with targeted analysis also avoids detection of pathogenic variants in genes that are not appropriate to detect in children for ethical reasons—such as variants associated with adult-onset conditions—by analyzing only those genes of interest. The full panel is typically less expensive than running individual tests, but the lab provides results only for the requested test.

Some barriers to use of genomic sequencing in newborn screening programs remain, including uncertainties around the meaning of various gene variants, the cost of adding sequencing to already stretched public health programs, and long turnaround times (rapid sequencing, which is currently used in some acute settings, is too expensive for widespread use). However, these barriers will likely be overcome in the next decade or so.[9] When that happens, sequencing will be ready for use in newborn screening programs. Although it is unlikely to replace all existing screening tools—some metabolic screening will still be needed, as will hearing tests and oxygen measurement for critical congenital heart defects—sequencing with targeted analysis will become an important part of newborn screening in the future.

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