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Policy brief: Improve coverage of newborn genetic screening to include the Recommended Uniform Screening Panel and newborn screening registry

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Executive Summary

A major goal of newborn screening is to reduce morbidity and mortality in infants and children by identifying heritable conditions in which early treatment may improve a child's long-term health and survival. However, the number and type of heritable disorders included in newborn screening currently vary from state to state. Expert recommendations to screen for 34 core conditions and report on 26 secondary conditions were issued by the U.S. Department of Health and Human Services. This panel, known as the Recommended Uniform Screening Panel (RUSP), has not been adopted by all states thereby creating a geographic disparity in opportunities to receive timely intervention for potentially life-threatening heritable conditions. The Academy supports the recommendation to adopt the RUSP in newborn screening programs across all states and calls for the creation of a national newborn screening registry to improve monitoring of all affected infants. Further, the Academy recommends the extension of reporting and tracking to the 59 actionable variants when whole-genome sequencing is performed and supports the expansion of reporting as new actionable variants are detected.

Background

A major goal of newborn screening is to identify heritable conditions in which early intervention may improve a child's long-term health or survival (Solomon et al., 2012). The *Screening for Heritable Disorders* federal legislation was passed in 2000, and implemented in 2004, to enhance the ability of state and local agencies to provide screening and counseling, as well as health care services for newborns with actual or potential risk for heritable disorders (National Institute of Child Health and Human Development, n.d.). During that time, the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC, formerly known as the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children) was chartered to provide recommendations to the Secretary of the U.S. Department of Health and Human Services regarding conditions to include in universal newborn screening and identify technologies, policies, and standards to reduce morbidity and mortality of newborns who have, or are at risk for, heritable disorders (Advisory Committee on Heritable Disorders in Newborns and Children, Health Resources and Services Administration of the United States Department of Health and Human Services, 2009). The

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DACHDNC considers many factors when making recommendations on which tests to add into newborn screening programs including whether (a) there is an accurate and reliable test for the disease, (b) the child's life would be improved by early detection and intervention, and (c) diagnosis and treatment are cost-effective. In addition to these criteria, the DACHDNC considers clinically significant conditions to include definitive identification of carrier status (U.S. Department of Health and Human Services, Advisory Committee on Heritable Disorders in Newborns and Children, 2016). In 2008, the *Newborn Screening Saves Lives Act* (H.R. 3825, S. 1858) was passed by Congress to add grant programs for education, follow-up care coordination, and new technology for newborn screening, to improve laboratory quality standards, and further define the role of the DACHDNC (Advisory Committee on Heritable Disorders in Newborns and Children, Health Resources and Services Administration of the United States Department of Health and Human Services, 2009; National Institute of Child Health and Human Development, n.d.; Solomon et al., 2012).

In 2009, the DACHDNC and Secretary of Health and Human Services recommended all state newborn screening programs to adopt the RUSP, a 30 core condition panel with 26 secondary conditions (RUSP, 2016). Since that time, 4 additional core conditions have been added to make the RUSP a 34 core condition panel with 26 secondary conditions. Secondary conditions of the RUSP can be identified through the screening process of the core conditions and can cause significant morbidity and/or mortality if they are not detected early in life (Solomon et al., 2012). The DACHDNC routinely considers the evidence related to adding screening tests to the RUSP. Recommendations from the DACHDNC are sent to the Secretary of Health and Human Services to consider, and a final recommendation is provided by the Secretary to state public health departments.

Core and secondary conditions are assessed via tandem mass spectrometry (MS/MS) using the newborn dried blood spot (NDBS) (Taylor, Wright, Hickey, & Housman, 2017). Although potentially 50 treatable inborn errors of metabolism can be detected through MS/MS, most states only test for a subset of these conditions due to cost and low frequency of selected conditions in some regions. Genetic abnormalities that are associated with major alterations of biochemicals in the blood can be detected. Other treatable conditions, including sickle cell disease, congenital hypothyroidism, cystic fibrosis, and severe combined immunodeficiency, are screened in the blood spot using other kinds of tests, such as high-performance liquid chromatography of hemoglobin or chemiluminescence. Two additional screening tests (congenital hearing loss and critical congenital heart disease) require physical measurements rather than blood testing.

When positive results are detected using MS/MS, which typically includes retesting and second-tier testing for confirmation, DNA-based testing can be used to confirm a positive result on the same blood spot used for the initial testing. DNA-based testing can be done by polymerase chain reaction, sequencing individual genes, sequencing using gene panels (a group of genes), or whole-genome or exome sequencing. Currently, targeted sequencing is only used as a secondary method in newborn screening programs to confirm positive test results for genetic disorders such as cystic fibrosis or sickle cell disease.

A major consideration when sequencing large gene panels or genome wide is the frequent occurrence of "incidental findings" otherwise referred to as "secondary findings." These terms refer to when genetic variants of potential importance to the health of the child are identified but are unrelated to the disease for which testing is being performed. In 2013, the American College of Medical Genetics and Genomics (ACMG) published a recommended minimum list of 56 actionable genetic variants to be reported as incidental or secondary findings when performing clinical genomic sequencing to promote a system of standardized reporting (Green et al., 2013). A recent study found that more than 1% of the population carry pathogenic mutations in these genes and are at increased risk for common diseases regardless of whether the diseases are part of their family history (Natarajan et al., 2016). In 2016, the ACMG expanded this list of secondary findings to 59 actionable variants (Kalia et al., 2017).

Outside of research protocols, whole-genome sequencing is not yet used by newborn screening programs. Whole-genome sequencing has been shown, however, to improve the positive predictive value of prenatal genetic screening (Strom, Maxwell, & Owen, 2017) and may have similar applicability to newborn screening (Berg et al., 2013; Bodian et al., 2016). Inclusion of genome-wide sequencing performed as a component of newborn screening, or as part of the secondary testing procedures to confirm diagnosis, may be indicated. The use of whole-genome sequencing for confirmation of primary screening is reasonable when performed as part of a comprehensive program that includes genetic counselling, secure storage, public and professional education, and long-term follow up of genomic data, as new findings increase interpretability of results (Friedman et al., 2017; King & Smith, 2016). When whole-genome sequencing is used, the reporting of the currently identified 59 actionable variants is recommended, with the exception of parents who opt out of having the results returned to them (American College of Medical Genetics and Genomics, 2014). Additional actionable variants may be incorporated into this list in the future.

Nurses play a key role in newborn screening. They provide education and support to families as part of the care team and can help parents to understand the importance of detecting pathogenic variants that may predispose their child to a severe but preventable outcome (Taylor et al., 2017). Advanced practice nurses, especially nurse practitioners and certified nurse midwives, are care providers who assist in ensuring that