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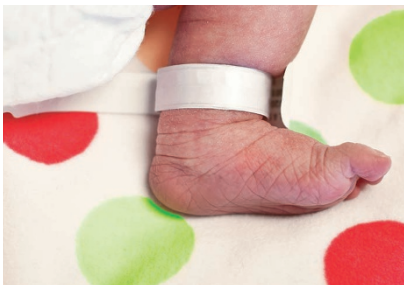

This issue of *Genetics in Medicine* is a themed issue, focusing on the most prominent success of our field in the realm of public health: newborn screening (NBS). From its early days, when testing for one or two rare diseases such as phenylketonuria and congenital hypothyroidism was first explored, NBS has grown to be a pillar of population health. Countless lives have been saved from premature death or profound disability through it.

The very success of NBS, coupled with new technologies able to diagnose a greater variety of disorders, has led to pressure to screen for an expanding array of diseases. A generation ago it was the advent of tandem mass spectrometry that presented opportunities and challenges. Now efforts are under way to investigate what role massively parallel sequencing could play in the NBS realm, an issue explored in a Commentary by Stephen Kingsmore and in research articles by Bodian and Baker and their colleagues. In addition to grappling with technical challenges, those in the field must also address ethical and policy issues. We seem to be having to learn the old lesson once again that just because a medical test is *possible* to perform it isn't always appropriate to do so—a point well made by David Dimmock (p. 218) in his Commentary on the article by Orsini et al. (p. 240) on screening for Krabbe disease.

It seems certain that NBS will play an increasing role in population health. Indeed, now that technology enables the detection of deleterious variants for adult-onset disorders, the field of NBS, with its long history of grappling with the challenge of how to choose which diseases to include in a population screen, is poised to inform emerging efforts to apply similar principles to the adult population. *—James P Evans, Editor-in-Chief*

Comparing genomic sequencing with metabolic screening of newborns

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As whole-genome sequencing (WGS) becomes less expensive and more widely available, its use has been called for in screening newborns for genetic disease. But few data have been available that compare standard newborn screening (NBS) currently in use with its WGS counterpart. In this issue, Bodian et al. provide a direct comparison, showing that NBS returns fewer false-negative results but more false positives, while WGS returns more results of uncertain significance (0.90% vs. 0.013%). The research study evaluated 1,696 ethnically and racially diverse newborns in Virginia, a state that routinely screens for 28 metabolic disorders and 4 hemoglobin defects. In the study population, five infants were diagnosed with a state-screened disorder. Of the five, NBS detected a disorder in four while WGS identified two. The authors point out that the debate over whether and when to implement NGS in newborn screening will require evidence-based evaluation of the two methods. Although WGS is technically feasible today, numerous ethical, legal, and social concerns must be addressed before any widespread testing could begin. For instance, WGS inevitably would generate results of unknown significance, results indicating defects with no known treatment, and defects in genes that lead to late-onset diseases. Sequencing that is more limited in scope, such as targeted gene panels, is under development and may address some of these issues. As the technology improves, studies such as this should be repeated. *—Karyn Hede, News Editor*

Sickle cell trait underestimated in Africa and the Middle East

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Mathematical models predicting how many infants will be born with sickle cell disease have grossly underestimated its prevalence in Africa and the Middle East, according to a new study. Using data from newborn screening (NBS) programs, Piel et al. suggest underestimates of roughly one-third in African populations and almost one-half in the Middle East. NBS detects the presence of hemoglobin S, a structural variant of normal adult hemoglobin caused by an amino acid substitution at position 6 of the β-globin gene. As is well known, the sickle variant protects against the most extreme symptoms of malaria and has therefore been under positive selection across malaria-endemic regions. Thus, the current mathematical model, using flawed assumptions of adherence to classical Hardy-Weinberg equilibrium, estimated that 305,800 infants would be born with sickle cell anemia in 2010. However, NBS data from 36 published studies demonstrated that many more infants were diagnosed with the disorder than predicted by such classic genetic modeling. In addition to selective pressures, the authors suggest that the discrepancy may be due in part to the extent of consanguineous marriage in the study areas. Further research may identify and quantify additional factors responsible for deviations from expected birth frequency. The authors suggest that NBS data offer "the unique advantage that they represent the best measure of true genotype frequencies," information of great relevance to health planning in such nations. *—Karyn Hede, News Editor*