To the Editor:

As a physician who primarily works in a neonatal intensive care unit (NICU) and whose patients are transferred from other hospitals, I spend a fair amount of time trying to hunt down newborn screening results. Sometimes this is in an effort to “cross my T’s and dot my I’s,” but on other occasions it is with the hope, sometimes desperate, that it will explain what is happening with my patient. More often than not, however, the results do not solve all my problems, and sometimes they create new ones I hadn’t anticipated. It is no wonder then that sifting through newborn screening results can sometimes be seen as a chore. How often do we really get a result that changes a patient’s life? The truth is, in the NICU, probably not often. My patients are already in a hospital with specialists at hand. Treatments are started and confirmatory testing is often sent before the newborn screen results are known; a positive screen is more a confirmation than a warning. But most children are not in a NICU when their first symptoms appear; they are out in the real world, where pediatricians are their first line of defense and the newborn screen result could be the difference between a timely diagnosis or not.

After reading the article “Updates in Newborn Screening” by Rajabi,1 I was reminded of how far we have come and just how much newborn screening programs have revolutionized the care of pediatric patients. In the 1960s, when testing for phenylketonuria (PKU) was first launched, a disease with a previously devastating prognosis could now be identified early enough that, with a relatively simple intervention, its neurologic devastation could be prevented.2 Newborn screening for PKU had the power to change a life. Since the 1960s, newborn screening has expanded exponentially, with the recommended uniform screening panel (RUSP) including 34 core disorders and 26 secondary disorders.3 The incidence of each individual disorder in itself is highly variable, but, when taken all together, they cover a significant proportion of children, and therefore, have a significant potential for impact.

Advances in medical technologies, testing modalities, and treatments have pushed the expansion of newborn screening. Diseases that were previously fatal can now be cured, or at least modified. Severe combined immunodeficiency (SCID), a heterogenous group of disorders all with a significant deficit of naïve T cells, is typically fatal early in life without timely identification and stem cell transplant. Early screening assays suffered from high false-positive rates, but in 2008 SCID screening was added to the Wisconsin newborn screen, showing that SCID could effectively be identified by the TREC (T-cell receptor excision circle) assay, with few false positives.4 Additionally, infants identified early and treated with a transplant had a markedly improved 2-year survival rate.4 This screen was recommended and accepted for addition to RUSP in 2010, and screening for SCID has now been implemented in all but three states.4 Screening has revealed a wider phenotypic spectrum with a higher incidence of T cell lymphopenias than previously known.

The newborn screen is indeed powerful. However, as with so many advancements in medicine, expansion has not come without controversy. Newborn screening is designed to identify patients with disorders that will present in early childhood and have a treatment that not only requires early detection but also provides a clear benefit. The expansion of newborn screening to include genetic diagnoses has stretched the goal of the screening program with the identification of carrier states. Such is the case with cystic fibrosis (CF). A positive screen for CF results in reflex testing of the most common gene alterations known to cause CF. Identification of only one gene defect does not rule out the diagnosis of CF, but it does confirm that at minimum the child is a carrier. This now goes beyond the purpose of early detection and spills over into the life of a child who may not want to know that he or she is a carrier.

Genetic testing is now cheaper and faster than it has ever been. The problem is that although the technology to sequence the human genome has advanced by leaps and bounds, our ability to interpret these results is much more limited.5 The human genome is massive, and it is well known that not all anomalies cause a clinical disease or syndrome. Some variants are well described, others less so; some will be novel, and many will have unclear clinical implications—a variant of unknown significance (VUS). In a sick infant, knowledge of a genetic cause could have a significant impact on their treatment, which may outweigh the risk of getting a VUS. What is the consequence of these findings in a healthy child? There is also the potential for findings that discover disease states that have no treatment, have a variable or adult onset, or have wide implications for entire families. The psychological burden of this kind of knowledge must also be con-
considered. Imagine knowing from their birth that your healthy child has the gene for a disease that is untreatable? Or growing up knowing you carry a genetic mutation that increases your risk for a serious illness? Would you spend your whole life worrying? How would that effect your quality of life? Would you have preferred not to know?

These, and many others, are questions that must be considered as we move into the era of personalized medicine. Although our goal as medical providers is to improve the lives of our patients, we must be careful to protect their rights to privacy, to well-being, and even to ignorance if they so desire.

REFERENCES

C. Lydia Wraight, MD
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Response:
Dr. Wraight’s letter lists many of the concerns brought by our pediatric colleagues working in the NICU. The NICU is a unique environment when it comes to newborn screening, as many of the interventions for preterm neonates lead to multiple false-positive results, and the neonates who do have an actionable condition on newborn screening are already being monitored closely. In the “real world,” we do indeed see the full spectrum of presentations, including many examples of the hope of newborn screening, which is intervention for an actionable condition before it is symptomatic.

However, we do have secondary and incidental results from newborn screening. We diagnose mothers with carnitine deficiency uncovered by newborn screening: clinical, biochemical, and molecular aspects. Genet Med. 2010;12(1):19-24. doi:10.1097/GIM.0b013e3181c5e67.