Debates about expanding newborn screening with whole genome sequencing are fueled by data about public perception, public opinion, and the positions taken by public advocates and advocacy groups. Given how the past can serve as a prologue for the future, however, one form of evidence that merits attention as we consider possible uses of whole-genome sequencing during the newborn period is parents’ (and children’s) diverse experiences with existing expanded screening protocols. What do we know about this experience base? And what implications might these data have for decisions about how we use whole genome sequencing and how we assess its impact in the future?

Expansion of newborn screening using next-generation sequencing raises numerous ethical and practical challenges, including the need to minimize potential harms to children, parents, and families. Although the broader literature on genetic susceptibility testing suggests that testing usually does not have adverse effects on children’s psychosocial well-being, certain newborn screening results have been demonstrated to cause distress, alter behavior, and even to influence the formation of new parental and family identities.

False-positive results are a case in point. Ever since the landmark study of parental anxiety in response to phenylketonuria (PKU) screening published in the 1960s, there has been debate about psychosocial harms of these newborn screening results. False-positive results have been generally associated with higher levels of parental anxiety and depression following newborn screening, and these elevated levels endured in some parents even after follow-up testing confirmed a true-negative result. Negative reactions were mitigated by quality education and communication about the implications of test results for the infant’s health from pediatricians (and other health professionals) at follow-up to initial screening. Still, the potential for negative psychological sequelae from false-positive results is a risk associated with any screening expansion—and broad-scale whole-genome sequencing for newborns would be on a scale far larger than any seen for this population.

The prospect of false-positive newborn screening results via genome sequencing raises concerns not just about parental mental health but also about overutilization of health services.

The adoption of next-generation sequencing technologies may also create unanticipated consequences for families with “true-positive” screens. Screening populations for rare genetic conditions changes the demographic make-up and disease profile of patients coming to the attention of clinicians. The adoption of a new technology called tandem mass spectrometry by newborn screening programs in the mid 2000s is instructive. The incidence of patients diagnosed with metabolic conditions via newborn screening was much higher than predicted based on clinical experience. Newborns registered out-of-range values at screening, but the question remained whether they were truly at risk for disease or if they constituted a new

and then told them that no one knows what the results mean and that there was nothing that could be done. Understandably, some parents became angry with the whole process.”11

Taken together, these data suggest that unanticipated harms of screening for Krabbe have been more common than expected and that its implementation may have been premature.

A further unintended consequence of expanded screening is the pressure it puts on available public health and clinical infrastructures. The screening itself is a quasiumiversal health service provided by state-sponsored public health programs in the United States, but medical follow-up is dependent on insurance status and thus not available to all. Existing screening has created situations where parents experience lack of access to proper medical care and treatment for conditions diagnosed through newborn screening;12 additional screening would likely further exacerbate this inequity.

Clinical implementation of exome sequencing has shown that these technologies create little distress for their intended diagnostic purpose, especially if the findings end diagnostic odysseys and provide access to a supportive community of similarly affected patients.13 However, these technologies also produce many uncertain or unanticipated results, as illustrated by the official reporting categories “variant of uncertain significance” and “incidental findings.” While patients tend to consent to receiving such findings, much more knowledge is needed about how these unclear and incidental findings change patients and families’ lives. As briefly summarized here, evidence about parental experiences with smaller screening expansions—those that plausibly forecast key implications of broader sequencing in the newborn period—suggest caution is merited. Ongoing investment in robust studies designed to illuminate the past and present impact of expanded screening on lived experience will be essential for guiding decisions about the future. In particular, it will be important to expand the methods employed (to narrative ethnography and randomized controlled trials, for instance), to increase the diversity of populations studied, and to focus beyond the individual level to families, communities, and health infrastructures.


