Newborn Screening for Neurodevelopmental Disorders May Exacerbate Health Disparities

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abstract

Newborn screening (NBS) began in the early 1960s with screening for phenylketonuria on blood collected on filter paper. The number of conditions included in NBS programs expanded significantly with the adoption of tandem mass spectrometry. The recommended uniform screening panel provides national guidance and has reduced state variability. Universality and uniformity have been supported to promote equity. Recently, a number of researchers have suggested expanding NBS to include genomic sequencing to identify all genetic disorders in newborns. This has been specifically suggested for genes that increase the risk for neurodevelopmental disorders (NDDs), with the presumption that early identification in the newborn period would reduce disabilities. We offer arguments to show that genomic sequencing of newborns for NDDs risks exacerbating disparities. First, the diagnosis of NDD requires clinical expertise, and both genetic and neurodevelopmental expertise are in short supply, leading to disparities in access to timely follow-up. Second, therapies for children with NDDs are insufficient to meet their needs. Increasing early identification for those at risk who may never manifest developmental delays could shift limited resources to those children whose parents are more poised to advocate, worsening disparities in access to services. Rather, we suggest an alternative: genomic sequencing of all children with diagnosed NDDs. This focused strategy would have the potential to target genomic sequencing at children who manifest NDDs across diverse populations which could better improve our understanding of contributory genes to NDDs.

Newborn screening for phenylketonuria using the Bacterial Inhibition Assay collected on filter paper (dried blood spots) in the early 1960s is often considered the birth of universal newborn screening (NBS) in the United States.[1] Later that decade, in 1968, Wilson and Jungner delineated 10 principles necessary to warrant population screening which was published as the World Health Organization's *Principles and Practice of Screening for Disease*.[2] Although not written specifically for NBS, the principles were adopted by many in the field. More than half a century later, they are still used with some modifications in NBS programs across the globe.[2]

In the early years of NBS, each additional condition required its own test. The application of tandem mass spectrometry to NBS in the 1990s provided a single platform that could screen for many conditions with one sample. Proponents of expanding NBS argued that this capability challenged some of the Wilson and Jungner criteria; for example, did the frequency of a condition matter if it were just added to a single platform technology that was already being used? Critics contended that such an expansion was premature because the screening would pick up more false-positives, fewer severe phenotypes, variants of unknown significance, and secondary conditions for which no treatment may exist. This could lead to financial and psychological costs associated with repeat

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testing as well as creating parental distress, stigmatizing labels, and/or "patients in waiting."[3]

Different states adopted tandem mass spectrometry at different rates throughout the 1990s and early 2000s such that there was great variability of the number of conditions a child was screened for depending on the state in which the child was born. In 2005, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children in conjunction with the American College of Medical Genetics and Genomics developed a list of conditions that should be included in state health newborn screening programs.[4] The development of the recommended uniform screening panel (RUSP) was criticized because it used a non-validated scoring system.[5,6] Over the next 17 years, however, the criteria have been scrutinized and formalized,[7,8] and the RUSP has expanded the number of conditions that are screened by using the dried blood spots. It has also expanded beyond the blood spot to include sensorineural hearing loss screening using Automated Auditory Brainstem Response, Otoacoustic Emissions, or both, and critical congenital heart defects using pulse oximetry. Today, in the United States, there is greater consistency between states than there was before the RUSP was promulgated, although adoption of the RUSP is not mandatory and states adopt new conditions at different speeds.[9] Additionally, some states include conditions that have not yet been approved (or have even been rejected) by the Advisory Committee on Heritable Disorders in Newborns and Children.[10]

The use of DNA testing in NBS was first adopted as second-tier testing for cystic fibrosis screening.[11,12] The inclusion of severe combined immunodeficiency syndrome into the RUSP was the first NBS test for which the primary analyte was DNA.[13] There are now proponents who argue to perform exome or genomic sequencing as part of NBS,[14] and explore the "revolutionary possibility of identifying all genetic disorders in newborns."[15] Others have ascertained parents' interest in whole-genome NBS, assuming future integration of whole-genome sequencing into public health programs.[14,16] However, at least to date, expansion to whole-genome sequencing has been rejected because of costs as well as unclear risk-benefit ratios.[17–19]

A more narrow proposal is to focus newborn sequencing to identify NDD.[20] Chung and colleagues have recently proposed large-scale pilot studies to explore the role of expanding NBS to screening NDDs at birth, arguing both that (1) the "improvement in medical, cognitive, and behavioral outcomes for these children" justifies newborn sequencing for NDDs, and (2) early screening would allow for increased understanding of the benefits of early diagnosis.[20] They proposed that early detection of NDD may improve access to educational plans, avoid long diagnostic pursuits, and prevent brain damage from inadequately treated seizures.[20]

At present, no specific panel for genetic evaluation of NDD exists because the spectrum of NDD is genetically and phenotypically heterogeneous with >2500 candidate genes.[21] Rather, the current clinical practice guidelines for children diagnosed with autism spectrum disorder, global developmental delay, or intellectual disability is to recommend testing simply with a chromosomal microarray for all children and Fragile X testing in boys.[22,23] However, chromosomal microarray testing only yields diagnostic clarification in 5.7% of NDDs,[24] whereas genetic testing with exome sequencing increases the diagnostic yield for children with NDD to 31%, and higher (53%) if children have additional associated conditions. To date, the experts remain divided about what genetic testing should be done in children who have been diagnosed with NDD. A convened expert panel from North America and Europe proposed using exome sequencing as a first-line evaluation for NDD,[25] although a more recent position statement from the Canadian College of Medical Geneticists recommended exome sequencing or a comprehensive gene panel only as second-tier testing by a clinical geneticist or metabolic physician for patients with global developmental disability or intellectual disability.[26]

Clinicians conducting genetic evaluations in the setting of diagnosed NDD face several practical barriers. First, it is recommended that a medical geneticist and/or certified genetic counselor should be involved with the interpretation of abnormal results (including variants of unknown significance) and subsequent counseling of families,[23] yet these specialists are in short supply.[27] Notably, this shortage creates disparities in access in several important ways: the geographic distribution of clinical geneticists limits access in rural communities,[28] and the lack of racial-cultural diversity within the workforce impacts its capacity to support minoritized and non-English-speaking populations.[29] Additionally, insurance coverage for chromosomal microarray testing often blocks testing even when clinically indicated for children with diagnosed NDD.[30]

Overall, completed genetic testing, even in patients diagnosed with autism, is low: only 16.5% in a large population-based study.[31] Patients diagnosed by a physician were more likely to have testing than those diagnosed by a psychologist,[31] suggesting that differences in subspecialist access have an impact on genetic testing receipt. However, even among NDD subspecialists, 10% and 40% reported not doing any genetic testing for a child with ASD with and without intellectual disability, respectively, which is contrary to practice guidelines.[32]

Genetic testing in the newborn period when phenotypic information is not available is less clear-cut than genetic testing a child after an NDD diagnosis is made clinically. Most developmental delays only emerge as developmental expectations rise over the first months and years of life. Because only the severest forms of developmental delay, those that impact feeding or central tone, will manifest clinically in the first weeks of life, interpreting the genetic information in the newborn period is less certain.

In fact, some children identified as having high-risk genetic variants may never express developmental delays or disabilities. Although the goal of NBS is to identify conditions before they express clinically to reduce adverse outcomes, it is questionable whether children identified to be at genetic risk of NDD will ever manifest developmental delays. Parents of these children may be angered by the anxiety that the results of the expanded NBS caused, the long-lasting stigmatizing and discriminatory effects on the child and family that labeling a child with an NDD engenders,[33] and how this knowledge may have impacted how they raised the child. Although parents do tend to value the increased benefit of additional screening over the risk of false-positive results,[34] early labeling of children may also cause harm due to the diagnosis becoming a self-fulfilling prophecy.[35] There is also the possibility that NBS for NDD will increase the risk of vulnerable child syndrome when parents have increased anxiety about their child's health, which modifies their behaviors toward the child and has been reported in other studies of cohorts with abnormal newborn screening results.[36] The problem is that without full clinical manifestations, diagnoses of many NDDs will not be definitive. Rather, children will sit in an at-risk area of developmental progress (mild delay or delay only in one developmental domain) making it hard to give them an appropriate label that will influence whether they are eligible for early intervention. At the other end of the spectrum, there will be the problem of false-negative results, whether due to the lack of comprehensive panels for NDDs or the lack of diagnostic certainty around many of the variants found in genes related to NDDs.[37] Parents of children with yet unidentified genetic causes of NDD may be falsely reassured by a negative NBS and fail to respond appropriately to delayed developmental milestones in later childhood.

There is also the potential for serious diagnostic inequities related to current genetic knowledge. To date, most genomic studies have involved few participants of non-European ancestry.[38] A recent study in the United Kingdom found lower diagnostic genomic yield of NDD in children from minoritized communities.[39] As such, genomic diagnosis may be skewed to newborns of European ancestry as has been seen in other genetic discovery studies,[40] who will then have greater access to early intervention, even if it is unclear that it is needed. Thus, genomic sequencing of newborns for NDDs has the potential to exacerbate health care disparities in both diagnosis and treatment.

This lower diagnostic yield in minoritized communities has been seen in other universal screening programs. For example, the diagnostic efficacy of comprehensive genetic testing for sensorineural hearing loss is lower for children of African ancestry and Hispanic ancestry.[41] In addition, lower diagnostic yield is compounded by the fact that even when near-universal newborn hearing screening rates are achieved, delays in diagnostic services and treatment are experienced by minoritized populations.[42] Similarly, minoritized populations did not see benefits when NBS programs were first mandated unless cooccurring with state Medicaid expansion.[43] Solving disparities in access after NBS initiatives are critical. Therefore, expanding NBS to screen for NDD may exacerbate disparities in minoritized communities if there is inadequate access to follow-up for definitive diagnoses and therapies.

Although we agree that identifying NDDs is important for individuals, families, and broader public health, we, as pediatricians, adopt the position of Brosco et al, who argued that "as NBS programs evolve, we must ensure that they continue to reduce the persistent health disparities among historically underserved populations."[44] Adopting this position, we argue that expanding NBS to include genomic sequencing for NDDs fails to account for workforce factors that have the potential to exacerbate inequities for underserved populations.

First, there is a lack of adequate diagnosticians to confirm NDDs, which are clinical diagnoses requiring neurodevelopmental testing and clinical expertise. Expanding demand through the identification and referral of children at risk for NDD based on a gene panel when some may never express delays would worsen the shortage. Over the last 10 years, the Developmental and Behavioral Pediatric workforce has only added 30 to 42 new specialists nationally each year,[45] which likely does not even replace the rate at which specialists are predicted to retire.[46] Alarmingly, these shortages do not impact all children equally, and there is evidence that Black and Hispanic children are less likely to obtain an autism diagnosis than white children.[47–49] This may be particularly true for children with comorbid intellectual disabilities.[47,50]

Second, the genetics workforce is insufficient to meet current demand, and expanding demand through broad NDD NBS would worsen the shortage. A 2019 workforce survey revealed not only long waiting times for initial appointments but clinical genetics job vacancies throughout the country.[51] The data reveal there were ~4700 certified genetics counselors in the United States in 2019 and 1240 medical geneticists as of April 2020.[52] Although this is an increase over the past decade for both sets of providers, there are geographic disparities with greater supply in the Northeast and some Midwestern and Western states and few in Southern states. There are also great disparities within states; a study in California found the genetic workforce concentrated in large cities leaving rural areas underserved.[53] Remote health care options may provide some help. However, most troubling are the racial and ethnic disparities that exist in access to genetic referral, testing, and counseling because of a complex interplay of health care access, insurance, and provider and patient-level factors.[54]

Third, there is a shortage of adequate therapists to meet the current needs of children with developmental delays in early childhood. Expanding NBS to identify children at

genetic risk for NDD will only exacerbate disparities because at-risk and affected children will now compete for providers and services. Data reveal that children whose caregivers have higher educational attainment, higher income, and are of white non-Hispanic ethnicity are more likely to get services.[55,56] Thus, at-risk children from more resourced families may successfully advocate for services over symptomatic children from less resourced families. Our current NBS system fails to appropriately funnel children to therapy services. Part C of the Individuals with Disabilities Education Act requires states to serve children with conditions with a "high probability of resulting in a developmental delay."[57] However, in practice, most NBS conditions associated with high risk for developmental delays are not on states' Established Condition lists for automatic early intervention qualification, and there is great variability between states.[58]

The expansion of NBS to include genomic sequencing for NDD ignores the fact that genetic risk for NDD is only one risk factor and, likely, not the largest. The focus on the genetics of NDD distracts from the known contributions of biological vulnerability (eg, prematurity[59,60]) and environmental vulnerabilities that interact and associate with developmental outcomes (eg, maternal education status,[61,62] exposure to adverse childhood events,[63] quality of home learning and family environment,[64] and access to quality early child care.[65]) Children with these known risk factors for developmental delay often fail to receive appropriate interventions to promote catch-up development. Although Part C of the Individuals with Disabilities Act mandates that states provide services for children <3 years of age with developmental delay, stark disparities exist in receipt of Early Intervention services by both race and family income.[55,66] Early head start programs currently serve <40% of the number of 3- and 4-year-olds in poverty and <5% of the number in poverty <3 years of age, with national variation in program participation.[67]

Realistically, expanding NBS recommendations will not change state practices uniformly. Each state independently establishes what conditions to include in its NBS panel, and the process for adding conditions varies between states.[68] States with smaller budgets for the NBS program may be less equipped to both expand and deliver the necessary follow-up services.

An alternate strategy that may have the potential to improve our knowledge of genetic etiologies for NDD across racial and ethnic groups would be to conduct genomic sequencing for NDD on all children who actually manifest developmental delays and have an NDD diagnosis. This recommendation is aligned with recent subspecialist-informed consensus recommendations which have suggested expanding diagnostic testing to include exome sequencing.[69] Expanding diagnostic genetic testing to all children who have been diagnosed with NDD, defined as children with intellectual disability, global developmental delay, or autism spectrum disorder, would confer 3 critical benefits. First, targeting testing to children who have already manifested delays in development would result in a higher positive predictive value compared with testing a general newborn population, thereby reducing the number of families who receive a false-positive genetic test. For these children and families, the burdens of worry and stigma related to developmental delay are already present even without a definitive etiology for their child's NDD. Although overall, it has been found that receiving a genetic diagnosis for their child is a difficult experience for families,[70] obtaining a definitive diagnosis can provide some clarity and relief.[71] A definitive diagnosis often makes the child immediately eligible for services, whereas a child diagnosed with general developmental delay may still have to meet the required thresholds of delay severity to qualify.[72] Those with NDD who do not get a genetic diagnosis will not be penalized because they will merit services on the basis of their phenotype. Second, genome sequencing for children with intellectual disability increases diagnostic yield and reduces time to genetic diagnosis, thus enabling these families to make decisions informed by genetic information for the child and family sooner.[73] Third, testing children with NDDs has the potential to mitigate current disparities in access to sequencing, which may help determine which variants are associated with more severe symptoms in children from diverse ethnic and racial backgrounds.

CONCLUSIONS

Sequencing has the potential to reduce health care disparities and improve outcomes if used strategically. Targeting sequencing to children who manifest developmental delays will improve the diagnostic validity of NDD genetic variants in children from all racial and ethnic communities. In so doing, we will learn the genetic causes of developmental delay in diverse populations which could better improve our understanding of contributory genes to NDD. Timely referrals for diagnostic workups and therapeutic services for children from all racial, ethnic, and socioeconomic backgrounds have the potential to reduce disparities in long-term developmental outcomes for vulnerable children with NDD.

ABBREVIATIONS

NBS: newborn screening
NDD: neurodevelopmental disorders
RUSP: recommended uniform screening panel

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