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INVITED REVIEW

Delivering paediatric precision medicine: Genomic and environmental considerations along the causal pathway of childhood neurodevelopmental disorders

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Precision medicine refers to treatments that are targeted to an individual's unique characteristics. Precision medicine for neurodevelopmental disorders (such as cerebral palsy, attention-deficit/hyperactivity disorder, obsessive–compulsive disorder, Tourette syndrome, and autism spectrum disorder) in children has predominantly focused on advances in genomic sequencing technologies to increase our ability to identify single gene mutations, diagnose a multitude of rare neurodevelopmental disorders, and gain insights into pathogenesis. Although targeting specific gene variants with high penetrance will help some children with rare disease, this approach will not help most children with neurodevelopmental disorders. A 'pathway' driven approach targeting the cumulative influence of psychosocial, epigenetic, or cellular factors is likely to be more effective. To optimize the therapeutic potential of precision medicine, we present a biopsychosocial integrated framework to examine the 'gene–environment neuroscience interaction'. Such an approach would be supported through harnessing the power of big data, transdiagnostic assessment, impact and implementation evaluation, and a bench-to-bedside scientific discovery agenda with ongoing clinician and patient engagement.

Precision medicine refers to treatments that are tailored or targeted to the needs of the individual based on their genetic, biomarker, phenotypic, and/or psychosocial characteristics.[1] While having an established history in fields such as paediatric oncology, with a focus on identifying specific biological mechanisms and molecular pathways to provide specific treatment recommendations and improve outcomes in childhood cancer,[2] precision medicine is increasingly being applied across other paediatric fields, including for children with neurodevelopmental disorders. Globally it has been estimated that there are 53 million children and young people who have a neurodevelopmental disorder.[3] They have a range of diverse symptoms and syndromes related to problems of neurodevelopment including epilepsy, common monogenic neurological disorders (e.g. Fragile X, Rett syndrome), rare genetic disorders, intellectual disability, cerebral palsy, autism spectrum disorder, Tourette syndrome, obsessive–compulsive disorder, and attention-deficit/hyperactivity disorder.[4] Although children and young people with neurodevelopmental disorders show great resilience across the life course, they are more likely to have higher levels of physical and mental health morbidity and mortality, are less likely to complete education, and are more likely to be unemployed and be socially isolated.[5] This not only results in a poorer quality of life for the individual but also a loss of productivity and increased health and welfare expenditure costs at a societal level.[5,6] In this narrative review we aim to highlight the current challenges and the therapeutic potential of precision medicine in neurodevelopmental disorders. We present a biopsychosocial integrated framework to examine the 'gene–environment neuroscience interaction'. We highlight the need for the power of big data, transdiagnostic assessment, impact and implementation evaluation, and a bench-to-bedside scientific discovery agenda with ongoing clinician and patient engagement.

What this paper adds

- Precision medicine has predominantly focused on genetic risk factors.
- The impact of environmental risk factors, particularly inflammatory, metabolic, and psychosocial risks, is understudied.
- A holistic biopsychosocial model of neurodevelopmental disorder causal pathways is presented.
- The model will provide precision medicine across the full spectrum of neurodevelopmental disorders.

ADVANCES IN PRECISION MEDICINE FOR NEURODEVELOPMENTAL DISORDERS

Recently, precision medicine for neurodevelopmental disorders has predominantly harnessed advances in genomic sequencing technologies to increase our ability to identify single gene mutations, diagnose a multitude of rare neurodevelopmental disorders, and gain insights into pathogenesis.[1] There have been clear successes in the application of such a precision medicine approach to monogenic neurodevelopmental disorders. Paediatric monogenic neurological disorders affect around 1% of children at birth, and neurological disorders in general are the primary cause of disability in global burden of disease analysis.[7] For those with monogenic disorders, early molecular diagnosis is important for genetic counselling and patient management.

Spinal muscular atrophy is an exemplar of a monogenic neurodevelopmental disorder, in which identifying and understanding the genetic underpinnings has driven development and clinical translation of genetic therapies across the spectrum of phenotypes, together with population screening imperatives to prevent and mitigate disease burden. This has especially transformed the lives of young children with spinal muscular atrophy, who no longer have a condition with progressive decline in motor function, with presymptomatic infants treated with disease modifying therapies attaining independent walking. Consequently, newborn screening programmes for spinal muscular atrophy have been implemented and welcomed by families and health professionals alike,[8] to improve equitable care, and optimize outcomes and cost-effectiveness.[9] Likewise, robust clinical trial pipelines targeting multiple physiological pathways to safely reduce progression, stabilize, or improve function across diverse neuromuscular disorders are emerging, including Charcot–Marie–Tooth disease, congenital myasthenic syndromes, muscular dystrophies, and congenital myopathies.[10]

Although advances continue to be made for monogenic neurodevelopmental disorders, the diagnostic yield of whole exome or genome sequencing depends upon the disorder. Disruptions in more than 900 different genes that contribute to brain development and function are reported among neurodevelopmental disorders.[11] Examples of the diagnostic yield of genomic testing (Table S1 and Table S2) found the proportion of patients with a 'monogenic' cause of their neurodevelopmental disorder varies by the diagnostic category. Notably, some studies target recruitment of high-risk subpopulations and thus the diagnostic yield for the total population may be lower than reported in these tables. So, while for some neurodevelopmental disorders, such as intellectual disability, advances in next generation sequencing technologies have increased diagnostic yield to more than 40%, this is not the case for many neurodevelopmental disorders that are common including attention-deficit/hyperactivity disorder, obsessive–compulsive disorder, Tourette syndrome, and autism spectrum disorder. Furthermore, a confirmed genetic diagnosis in a neurodevelopmental disorder will only provide an effective targeted 'precision' treatment, such as vitamin supplementation, cofactor, enzyme replacement, pharmacological or genetic therapies for less than 10% of individuals at present. A monogenic diagnosis does however enable prospective reproductive decision-making for parents, facilitated through genetic counselling.[1,12] While common genetic variants have been identified as important and cumulative contributors

to their pathogenesis as outlined in Table S2, most children with neurodevelopmental disorders are likely to have multiple genes with small contributions, so gene therapy may not address their therapeutic needs, even in the future. This highlights the need for a broader conceptualization of precision medicine in neurodevelopmental disorders.

THE ROLE OF ENVIRONMENTAL FACTORS IN THE CAUSAL PATHWAY OF NEURODEVELOPMENTAL DISORDERS

Establishing genotype–phenotype correlations in neurodevelopmental disorders has been difficult. For example, two or more phenotypes may occur in an individual because of the convergence of pathogenetic processes between different neurodevelopmental disorders.[13] Thus, it is more likely the complex interaction of genetic and environmental factors encompassing inflammatory, metabolic, and psychosocial pathways influence the phenotypic expression of neurodevelopmental disorders.[14]

Inflammation and metabolic risk factors during pregnancy

Pregnancy associated factors have been a major focus of research of in utero environmental influences, given the major neurodevelopment that occurs in the womb. Over recent decades, clinical and population studies and meta-analyses of case–control studies have highlighted the role of inflammation and metabolic risk factor exposure in utero in the causal pathway for neurodevelopmental disorders.[15–17] These human studies have been complemented by animal studies which have the potential to explore crosstalk between the peripheral immune system and the central nervous system.[16] Environmental factors may mediate the regulation of gene activity through epigenetic processes, such as DNA methylation or histone modification.[16] A recent systematic review of population studies and meta-analyses highlighted that many maternal factors present during pregnancy statistically increase the risk of neurodevelopmental disorders in offspring, including maternal obesity, gestational diabetes, preeclampsia, smoking, anxiety/depression, psychosocial stress, autoimmune disease, asthma, and infection. These factors individually increase the risk of neurodevelopmental disorders in offspring by 30% to 80% (Figure S1).[15] These factors were agnostic to the specific neurodevelopmental disorder, meaning the effects were the same for autism spectrum disorder, attention-deficit/hyperactivity disorder, Tourette syndrome, and other neurodevelopmental disorders.[15] It is likely that the risk is cumulative, meaning multiple risk factors are interacting.[15,16]

This risk may be further compounded by perinatal and postnatal pro-inflammatory events that may be experienced by the child including preterm birth, birth asphyxia, infection, and brain injury.[16] It is unclear how these maternal factors result in increased risk in offspring, and is likely to be multifactorial with immunogenetic, inflammatory, metabolic, and epigenetic mechanisms all possible. For example, brain transcriptomic studies in autism spectrum disorder, cerebral palsy, Tourette syndrome, and obsessive–compulsive disorder all demonstrate that the most upregulated gene pathways in the brain are inflammatory.[15–18] At this time, however, there are no approved therapies that specifically target inflammation as a causal pathway in neurodevelopmental disorders, although anti-inflammatory umbilical cord blood stem cells for children with cerebral palsy have shown efficacy in phase 2 trials with regulatory approvals currently being sought.[19]

Psychosocial risk factors

Studies have shown that children with psychosocial risk factors including those who experience poverty and adverse childhood events have a higher risk of a neurodevelopmental disorders, compared to their more advantaged peers.[20,21] For example, children with cerebral palsy who live in disadvantaged neighbourhoods in Australia and Canada are up to 50% more likely to have severe physical and intellectual disability compared to children with cerebral palsy who live in advantaged neighbourhoods.[20,21] The impact of neighbourhood disadvantage has been found in Canada to be mediated by maternal education level, with the higher the maternal education, the milder the physical disability.[21] Animal models suggest that the stress on a pregnant female from psychosocial risk factors such as poverty, poor maternal mental health, and family dysfunction may impact through epigenetic mechanisms and by increasing in utero inflammation.[22] With epigenetics being a burgeoning area of research in neurodevelopmental disorders, there is a growing body of evidence that personalized environmental enrichment such as parent training, functional and task-based training to intensify child-initiated motor, cognitive, sensory, and social learning, can improve outcomes in children with some forms of neurodevelopmental disorder.[23] However, there is increasing evidence that families experiencing psychosocial stressors have less capacity and resources to provide psychosocial stimulation and there are structural barriers to their access to services for their child with a neurodevelopmental disorder.[24]

BROADENING THE PERSPECTIVE OF PRECISION MEDICINE FOR NEURODEVELOPMENTAL DISORDERS USING A 'BIOPSYCHOSOCIAL FRAMEWORK'

To ensure that all children with neurodevelopmental disorders benefit from precision medicine, we propose a research framework that examines the 'gene–environment neuroscience interaction'. If we examine the relationship between single risk factors and neurodevelopmental disorders as it is currently done, we fail to consider the complex

biopsychosocial interplay between genomic or environmental factors.[25] This results in a fragmented genetic and environmental research agenda and limits opportunities for therapeutic discovery. Precision medicine research strategies guided by the biopsychosocial model of child development developed by Bronfenbrenner could significantly improve personalized therapeutic approaches for neurodevelopmental disorders (Figure 1).[26] This model focuses on the multifactorial and dynamic relationships between the child and their environment in the critical therapeutic window of neuroplasticity in early childhood. It examines the allostatic load of co-occurring factors that are in the immediate environment (proximal factors, e.g. genetic variant) or operate less directly (distal factors, e.g. psychosocial risk), and the amount of risk and protection these factors confer on an individual. For example, a genetic variant may not be enough to express a disease, but when combined with an environmental risk, this may result in a severe and limiting neurodevelopmental disorder for that child.[25] These gene–environment interactions must be considered in precision medicine if outcomes of neurodevelopmental disorders are to be optimized.

The case study below (names and details have been changed) describes this complexity and highlights that for a child with spinal muscular atrophy about to receive gene therapy to restore *SMN* gene function, environmental risk factors could also influence the course and outcome. Although spinal muscular atrophy gene therapy fits the traditional definition of precision medicine, treating the genetic variant will only address one challenge this child will face as they develop. The integration of tailored inflammatory, metabolic, and psychosocial care and support are essential in this case to optimize health outcomes with advanced therapies.

Case study illustrating the need for a biopsychosocial model of precision medicine

Sam is a young male who lives in a rural farming area, 400 km west of Sydney, Australia. When he was just 8 days old, Sam's newborn screen was positive for spinal muscular atrophy, with a genotype of *0SMN1* and *2SMN2*. The paediatrician from the rural hospital Sam was born at notified his mother and, while Sam appeared healthy and well, strongly advised them to travel to Sydney as soon as possible for confirmatory testing and specialist neuromuscular consultation.

Sam's parents had never heard of spinal muscular atrophy and felt overwhelmed by the news they had just received. Sam's mother was not only recovering from a high-risk pregnancy due to several underlying health problems, but additional complications from birth left her unfit to immediately travel long distances by car. Furthermore, Sam's father was responsible for running and maintaining their struggling family farm in the height of ongoing New South Wales droughts. These concerns, alongside broken extended family relationships that left no one to care for their older children, resulted in it taking 5 days to take Sam to Sydney for medical care.

Sam's neurological assessment on day 13 identified hypotonia, hip flexion weakness, and areflexia. Sam was treated with gene therapy, requiring him to stay close to Sydney for nearly 6 weeks. Navigating Sam's diagnosis was difficult on

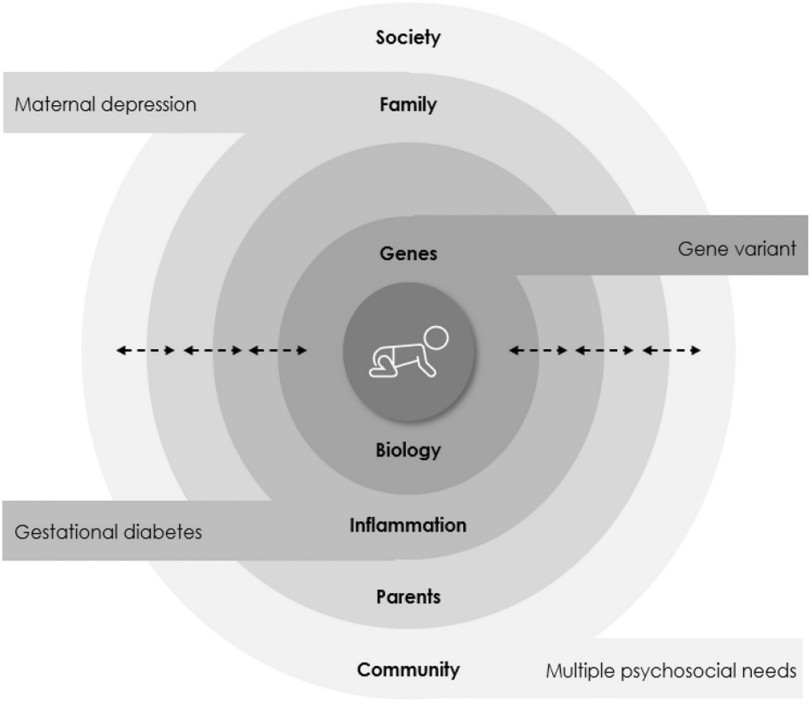

FIGURE 1 Biopsychosocial model of neurodevelopmental disorder causal pathways.

the family. Because of financial and work pressures, Sam's father and siblings quickly returned home, leaving him and his mother in Sydney to continue treatment. Doing it alone, alongside the angst of having a newborn infant with a rare disease, took a toll on Sam's mother. She had little to no social support and quickly saw the re-emergence of the postnatal depression that she had suffered after her first pregnancy as a teenager. After Sam's initial treatment in Sydney, the dire state of his mother's mental health made it difficult for her to advocate and provide for his needs after returning home.

Over the first few years of Sam's life, several ongoing psychosocial factors hindered his ability to develop and thrive. Living in a rural area created barriers to obtaining regular medical and allied health care. Travelling to medical, physiotherapy, or occupational therapy appointments was a whole day round trip for Sam's parents, sometimes resulting in delayed visits or non-attendance. The strain that having a child with additional needs put on Sam's parents' relationship contributed to their separation before Sam's first birthday. Sam's father quickly found himself in a new relationship, leaving Sam's mother to move him and his siblings into the local town, and, on a single income, rent a small house without disability access. The mental health of Sam's mother continued to deteriorate and, because of their location, she struggled to access the psychological support she needed. She often turned to excessive alcohol consumption as a coping mechanism, and over time struggled to find the motivation needed to navigate the National Disability Insurance Scheme required to support Sam's ongoing needs.

Despite receiving accurate diagnosis through 'precision medicine' as a newborn infant for spinal muscular atrophy, a plethora of other psychosocial and environmental factors delayed initial treatment for Sam, compromising his ongoing development and care resulting in a suboptimal treatment response to his 'state of the art' genetic therapy (three spinal muscular atrophy therapies have been approved over a 4-year period, offering different options for treatment with differing routes and frequency of administration). However, a biopsychosocial precision medicine approach with dynamic and longitudinal transdiagnostic assessments and tailored psychosocial interventions to modify environmental aspects are expected to positively impact his life course trajectory and optimize his long-term outcomes.

OPPORTUNITIES AND CHALLENGES FOR FUTURE TRANSLATIONAL RESEARCH ACROSS NEURODEVELOPMENTAL DISORDERS

Only by considering the interaction of genes and an array of environmental factors can we truly understand causal pathways and develop a therapeutic approach that benefits all children with neurodevelopmental disorders. This is exemplified by progress in understanding the complex factors leading to the development of cerebral palsy, contributing to reduced rates and improvements in outcomes in the most common cause of brain injury in childhood.[27] The targeting of multiple causative factors from preconception onwards has resulted in improvements in antenatal and neonatal intensive care, maternal and infant vaccination programmes, reduced odds of multiple pregnancies with assisted reproductive technologies, corticosteroids for preterm birth, rhesus immunoglobulin for ABO incompatibility, therapeutic hypothermia for hypoxic ischaemic encephalopathy, and strategies for early detection and targeted early intervention.[27]

Without this biopsychosocial approach, scaling up genomic and biological precision medicine advances may also exacerbate the existing health inequities in neurodevelopmental disorders because of financial, cultural, and linguistic barriers to accessing novel gene therapy for example, which have become more stark with the COVID-19 pandemic.[21] We propose the following elements are essential for this holistic vision for precision medicine as outlined in Figure 2.

Using transdiagnostic assessment tools for researchers and clinicians that incorporate the gene–environment interaction on neurodevelopmental disorders

The majority of children with neurodevelopmental disorders are described according to the cluster of symptoms (such as obsessive–compulsive disorder or cerebral palsy), which provides minimal insight into pathophysiology, although does provide some limited therapeutic guidance. The identification of missing heritability, polygenic, and multifactorial factors along the causal pathway for common neurodevelopmental disorders, and an understanding of how they interact in the diagnostic process, is critical to understanding causal pathways and developing therapeutic responses. A streamlined, standardized transdiagnostic approach is needed using validated measures for genetic, inflammatory, metabolic, and psychosocial risks and their influences longitudinally and dynamically, commencing from pregnancy for children at risk of/with neurodevelopmental disorders to direct a precision medicine approach to therapeutic options.[28]

Measuring the cumulative interaction between gene–environment using big data

A comprehensive approach to integrating genomic, neuroimaging and neurophysiology, inflammatory, metabolic, and psychosocial data collection is needed. Advances in high throughput sequencing technologies (genomics, transcriptomics, proteomics, etc.) have enabled the generation of extensive biological data sets, requiring bioinformatic analysis, with an emphasis on identifying shared pathways and therapeutic targets. Interdisciplinary collaboration and an integrated approach, incorporating 'big data' with phenotypic features and environmental exposures, is important to improve the understanding of complex neurodevelopmental processes and

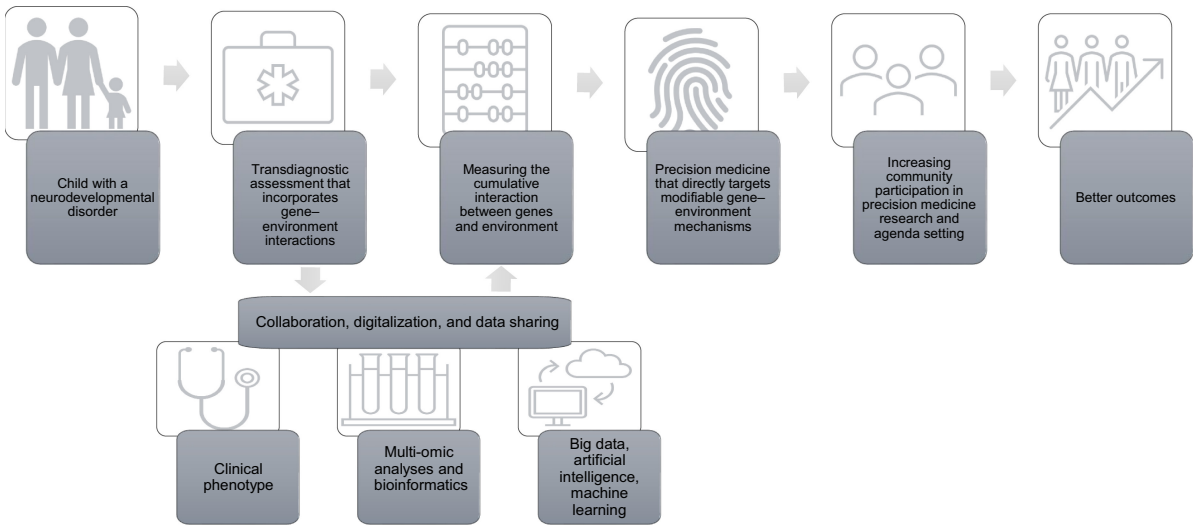

FIGURE 2 A biopsychosocial approach to precision medicine in neurodevelopmental disorders.

adaption to internal and external changes. This approach requires a systematic, comprehensive, and consistent data framework. Analysis of large and complex neurodevelopmental disorder cohorts and data sets will require combinations of expertise in clinical, laboratory, and population (gen) omics, software design, and bioinformatics as well as artificial intelligence and machine learning approaches to identify gene–environment associations at scale. Standardized and internationally accepted terminology is critical for minimal and advanced data sets, incorporating diagnosis, natural history, quantification of severity, and exposures. This requires further development of universal, acceptable, age-appropriate, multidimensional, multidisciplinary, and sensitive metrics and tools embedded within clinical data sets.

Translating novel treatments from bench to bedside that directly target modifiable gene–environment mechanisms in precision medicine

At present, the disjointed approach to precision medicine for children with neurodevelopmental disorders runs the risk of failing to live up to its promise. Research is, on the whole, siloed with genetic, inflammatory, epidemiological, and psychosocial research occurring with little integration or collaboration. In addition, robust evidence of the efficacy and cost–benefit of precision medicine, though emerging, is currently absent.[29] A detailed and nuanced understanding of what it would take to mainstream tailored precision medicine into routine care has yet to be considered. Encouraging multidisciplinary collaboration of researchers through funding and institutional support across these streams is key to address these gaps.

This will improve efforts to develop therapeutic discoveries that reflect the causal pathways for the majority of neurodevelopmental disorders, including: (1) increasing our understanding of epigenetic regulation (histone acetylation, methylation), cell signalling, and cell activation (including inflammation); (2) enhancing therapeutic options to treat pro-inflammatory states; and (3) ensuring a holistic approach is used to address biopsychosocial risk factors. Given the polygenic and multifactorial nature of common neurodevelopmental disorders such as attention-deficit/hyperactivity disorder and Tourette syndrome, it is likely that a common pathway-driven therapeutic approach (targeting inflammation, epigenetic, metabolic, and psychosocial stress) will be therapeutically more relevant than targeting individual gene variants. For example, environmental enrichment in concert with interventions that promote neuroplasticity and accelerate learning in children with neurodevelopmental disorders are already underway with randomized controlled trials currently testing the efficacy of these combined approaches.[30] It is likely that such biopsychosocial interventions that provide targeted and personalized care will rapidly become available, making precision medicine standard care.

Increasing community participation in precision medicine research agenda setting

The benefits of a biopsychosocial model for precision medicine for neurodevelopmental disorders means that we work with people with lived experience to set research priorities. This has been used in cerebral palsy research to great effect. Key to this work is ensuring that people with lived experience of neurodevelopmental disorders are at the centre of priority setting and advances in precision medicine. Such a process needs to reflect the wide range of lived experience of people with neurodevelopmental disorders, their families, and clinicians so that there is equitable participation in research and access to new precision medicine discoveries.

CONCLUSION

In this age of emerging genetic and molecular therapies making previously untreatable disorders potentially treatable, never has it been more important to determine and expand on the 'causes' of disease, and the 'contributors' to severity and functional impairment beyond the genome. Targeting the cumulative interaction of genetic and environmental specific aetiological and pathophysiological pathways is inherently logical and reflects the lived experience of a child with a neurodevelopmental disorder. An integrated biopsychosocial model will further our understanding of causal pathways and the development of novel therapeutic approaches. It should inform all areas of discovery research, including driving grant funding and collaboration. To not do this runs the risk of an inequitable, ineffective, and inefficient translation of research findings for children with neurodevelopmental disorders and their families.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Association between maternal risk factors that are present in pregnancy and neurodevelopmental disorders in offspring.
Table S1: Recent yield of comprehensive whole exome/genome sequencing for various neurodevelopmental disorders.
Table S2: Diagnostic yield for genetic causes of neurodevelopmental disorders.

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