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Genetic Counseling in Neurodevelopmental Disorders

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Neurodevelopmental disorders (NDDs), including global developmental delay (GDD), intellectual disability (ID), and autism spectrum disorder (ASD), represent a continuum of developmental brain dysfunction. Although the etiology of NDD is heterogeneous, genetic variation represents the largest contribution, strongly supporting the recommendation for genetic evaluation in individuals with GDD/ID and ASD. Technological advances now allow for a specific genetic diagnosis to be identified in a substantial portion of affected individuals. This information has important ramifications for treatment, prognosis, and recurrence risk, as well as psychological and social benefits for the family. Genetic counseling is a vital service to enable patients and their families to understand and adapt to the genetic contribution to NDDs. As the demand for genetic evaluation for NDDs increases, genetic counselors will have a predominant role in the ongoing evaluation of NDDs, especially as identification of genetic etiologies has the potential to lead to targeted treatments for NDDs in the future.

Genetic counselors are increasingly becoming integral members of the team working with families facing a diagnosis of a neurodevelopmental disorder (NDD). Genetic counselors have many roles in this setting—helping families understand the NDD diagnosis and its implications for their child and family, providing education about potential etiologies and the role of genetics, and participating in the diagnostic evaluation. In addition, genetic counselors help families with making decisions related to genetics and adapting to the disability or genetic condition.

Herein, we will begin with a review of the definitions and etiologies of NDDs. We will provide an overview of diagnostic genetic testing for NDDs and then delve deeper into the numerous counseling issues that arise. Overall, this work will focus on genetic evaluation and counseling for NDDs that have the greatest likelihood to yield an identifiable genetic cause—namely, global developmental delay (GDD), intellectual

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disability (ID), and autism spectrum disorder (ASD)—highlighting the importance of genetic counseling and ongoing follow-up.

DEFINITIONS

NDDs are a common group of conditions that manifest as impairments in development and function that begin in childhood. As defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), NDDs include ID, ASD, attention deficit hyperactivity disorder, communication disorders, motor disorders such as cerebral palsy, and specific learning disorders (American Psychiatric Association 2013). These conditions are typically diagnosed after comprehensive assessments with a developmental pediatrician, pediatric neurologist, neuropsychologist, psychiatrist, or other specialist.

As defined by the American Association on Intellectual and Developmental Disability, ID (formerly called mental retardation) is "characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. The disability originates before age 18 years" (Schalock et al. 2007). Standardized measures of adaptive functioning and intelligence are typically reliable in children over age 5 years. Before that time, a diagnosis of GDD is often given when a child presents with significant delays in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living (Moeschler et al. 2014). Not all children diagnosed with GDD will meet diagnostic criteria for ID, particularly those who present with mild delays and who are expected to meet age-appropriate developmental milestones. The prevalence of GDD/ID in the United States is estimated to be 1%–3% (Moeschler et al. 2014).

ASD is characterized by deficits in social communication and interactions, along with restrictive, repetitive patterns of behaviors, interests, and activities (American Psychiatric Association 2013). This definition encompasses previously used terminology such as pervasive developmental disorder and its subgroupings (autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified). ASD is four times more common in males than females (Baio et al. 2018). The severity of the ASD diagnosis is based on level of support: Level 1 indicates "requiring support," Level 2 indicates "requiring substantial support," or Level 3 "requiring very substantial support" (American Psychiatric Association 2013). According to the Autism and Developmental Disabilities Monitoring (ADDM) Network study from surveillance year 2014, one in 59 children (1.7%) aged 8 years has been identified with a diagnosis of ASD (Baio et al. 2018).

NDDs often present with complex patterns of impairment across motor, cognitive, and neurobehavioral domains. For example, individuals with GDD/ID may show autistic features, which may or may not meet criteria for an ASD diagnosis. Likewise, approximately one-third of individuals with ASD have ID (Baio et al. 2018). Although cerebral palsy (CP) is often secondary to prenatal and/or perinatal brain injury, there are many genetic disorders that masquerade as CP and may also have ID and/or ASD as a feature (Lee et al. 2014b). Other medical comorbidities seen in NDDs include epilepsy, congenital anomalies, and psychiatric conditions (Schalock et al. 2007).

Ultimately, these various NDDs can be represented on a larger continuum of an underlying developmental brain dysfunction (DBD) (Moreno-De-Luca et al. 2013; Finucane and Myers 2016). Research has shown a shared genetic basis for ID and related disorders such as epilepsy, ASD, schizophrenia, and others that can be considered part of the spectrum of DBD (Vissers et al. 2016). There can be significant diagnostic overlap and co-occurrence of these brain-based diagnoses within an affected individual and/or among family members, which further points toward an underlying genetic contribution.

ETIOLOGY OF NDDs

The etiology of NDD is heterogeneous, including genetic as well as nongenetic factors. The

genetic contribution to NDDs is variable, but reports of increased rates of concordance for NDDs among twins and family members support a high degree of heritability (Chaste and Leboyer 2012). There is substantial genetic heterogeneity, as there are an enormous number of individually rare genetic conditions that present with an NDD as a prominent feature. These include chromosome copy number variants (CNVs) and single-gene disorders. Nongenetic factors may modify the manifestation of features, thus resulting in a multifactorial condition. Variable expressivity and reduced penetrance also impact the diagnosis and presence of medical comorbidities with NDD, especially within the same family. For example, the pathogenic 16p11.2 microdeletion has been reported in individuals with ASD, GDD/ID, and/or neuropsychiatric conditions, as well as apparently unaffected individuals (Ho et al. 2016). Other mechanisms include epigenetic alternations or a polygenic contribution with multiple common variants or polymorphisms collectively resulting in an NDD (Siu and Weksberg 2017).

Epidemiologic studies have attempted to establish the association of various environmental factors with NDDs, such as maternal health conditions, perinatal infection, malnutrition, trauma, and many others (Gentner and Leppert 2019). For instance, prenatal exposure to alcohol and environmental exposure to lead are confirmed to be associated with an increased risk for GDD/ID. On the other hand, any association between vaccines and ASD has been thoroughly debunked by many studies, including those conducted by the Centers for Disease Control (DeStefano et al. 2013).

The high diagnostic yield from genetic testing indicates that genetic variation has a larger causal contribution to the development of NDDs when compared with environmental risk factors. Indeed, modern techniques now result in the identification of genetic etiologies in more than half of individuals with severe GDD/ID (Gilissen et al. 2014), with that number expected to increase with improvements in technology and disease-gene discovery. Therefore, in the absence of a clear and substantial environmental factor that explains the clinical presentation, a genetic workup is appropriate to offer to individuals with GDD/ID and ASD.

GENETIC TESTING IN NDDs

Professional societies have published guidelines on genetic evaluation of GDD/ID and ASD. The most recent published guidelines were authored by the American College of Medical Genetics and Genomics (ACMG) for ASD (Schaefer et al. 2013) and by the American Academy of Pediatrics (AAP) for GDD and ID (Moeschler et al. 2014), and their recommendations are largely consistent.

As always, the evaluation should begin with review of the medical, developmental, and antenatal history, physical and neurologic exam, and review of three-generation family history. Keeping in mind the concepts of DBD as well as variable expressivity, family history queries should include conditions such as epilepsy, psychiatric disorders, and learning disabilities in addition to ASD and GDD/ID, especially with regard to parental abilities (Finucane and Myers 2016). If a specific diagnosis is suspected based on the history and exam, targeted testing could be performed for that disorder. If no specific diagnosis is suspected, both AAP and ACMG recommend a tiered approach to genetic testing.

There is widespread consensus that chromosomal microarray (CMA) testing should be the first-tier genetic test for any patient with unexplained GDD, ID, and/or ASD. The expected yield is ~10%, or possibly up to 15%–20% in patients with multiple congenital anomalies (Miller et al. 2010). G-banded karyotype is no longer recommended as a first-tier test unless there is suspicion of aneuploidy (e.g., Down syndrome) or a history of recurrent miscarriages (Miller et al. 2010). *FMR1* trinucleotide repeat analysis for fragile X syndrome is also recommended as a first-tier test for patients with nonspecific GDD, ID, and/or ASD. The expected yield is 1%–5% in males and lower in females.

The AAP and ACMG guidelines highlighted several other tests that could be considered as second-tier in patients with negative CMA and

fragile X testing. These included analysis of the *MECP2* gene in females (expected yield 1%–4%), analysis of the *PTEN* gene in patients with macrocephaly (expected yield 5%), and X-linked ID gene panels in males with positive family history. The guidelines also addressed screening for inborn errors of metabolism (IEMs). There remains a lack of consensus about the utility of routine IEM screening in patients with nonspecific NDD. The overall expected yield is relatively low, <5%, but IEMs are considered high-impact as some have targeted treatment (van Karnebeek et al. 2014). Indications that should prompt consideration of IEM include developmental regression (beyond the typical loss of speech that may occur at 18–24 mo in ASD), multisystem involvement, failure to thrive, specific dietary triggers, and seizures, among others. Neuroimaging via brain magnetic resonance imaging (MRI) is an important part of the workup in patients with NDDs who have an abnormal neurologic exam, micro- or macrocephaly, regression, and/or seizures. Otherwise, brain MRI is not performed routinely in individuals with NDDs because of the low yield in absence of specific indicators, as well as the need for sedation.

At the time these guidelines were published, next-generation sequencing (NGS) techniques were still relatively new and, accordingly, the AAP and ACMG did not recommend exome sequencing (ES) in the diagnostic evaluation of patients with NDDs. ES became clinically available in late 2011, and, initially, it was typically ordered for patients as a last resort after extensive other investigations failed to uncover the diagnosis. However, in recent years, substantial literature has been published regarding the diagnostic yield, clinical utility, and cost effectiveness of ES in individuals with NDDs. Numerous studies have found a high diagnostic yield of ES—potentially >40% in patients with ID and other NDDs, especially when performed as a trio including both biological parents—with frequent changes to medical management (Lee et al. 2014a; Srivastava et al. 2014, 2019; Kuperberg et al. 2016; Nolan and Carlson 2016; Clark et al. 2018; Wright et al. 2018). Several cost-effectiveness studies have found that using ES early in the diagnostic pathway markedly increases the diagnostic rate while reducing the cost per diagnosis, resulting in an overall cost savings compared with traditional diagnostic trajectory of sequential testing with or without ES as last resort (Monroe et al. 2016; Stark et al. 2017). Given the rapid pace of disease gene discovery, it is recommended to periodically reanalyze the exome data for individuals without a definitive diagnosis, because evidence suggests that doing so may increase the diagnostic yield by 10% or more (Wenger et al. 2017; Al-Nabhani et al. 2018).

These data strongly support the use of ES as a second-tier test in patients with NDD (see Box 1). Indeed, this has become standard practice in many centers across the United States, and it is anticipated that the next updates to the guidelines will reflect this. One caveat is that the expected diagnostic yield of ES in patients with isolated ASD (i.e., without cognitive impairment or morphologic abnormalities) is much lower (3% in one study) than in patients with ID or more complex presentations (Tammimies et al. 2015); therefore, at this time it is reasonable to offer CMA and fragile X, but not ES, to patients with isolated ASD.

Although genome sequencing (GS) is primarily used in research settings at this time, it is expected that this too will become a routine clinical test. GS has advantages over both CMA and ES, including more even coverage across the genome, analysis of noncoding regions, and ability to detect CNVs and structural rearrangements with specific breakpoints (Hehir-Kwa et al. 2015). GS may also be able to detect pathogenic short tandem repeat expansions, which underlie a number of Mendelian diseases including some NDDs such as fragile X syndrome (Dashnow et al. 2018).

Notably, there is emerging evidence based on two recent meta-analyses that ES and possibly GS should be considered as a first-tier test for the diagnostic evaluation of individuals with NDDs. Clark et al. (2018) conducted a meta-analysis of 37 studies encompassing 20,068 children with a range of indications including NDDs and found that the diagnostic yields of GS (41%) and ES (36%) were substantially

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BOX 1. GENETIC TESTING IN NDDs

The following tests are frequently offered to individuals with NDDs in whom a specific diagnosis is not suspected after history and exam:

- Chromosomal microarray (CMA)
- *FMR1* trinucleotide repeat analysis for fragile X syndrome
- Exome sequencing (ES)

The current practice in most centers is to begin with CMA and *FMR1* testing, followed by ES as second tier; however emerging evidence supports the use of ES as a first-tier test.
Other tests to consider as indicated based on clinical presentation:

- Screening for inborn errors of metabolism
- Brain MRI for patients with abnormal neurologic exam
- Testing for specific Mendelian disorders

greater than CMA (10%) in these children with suspected genetic diseases. Furthermore, in this meta-analysis, the clinical utility, defined as change in clinical management, of GS (27%) and ES (17%) were higher than of CMA (6%). Srivastava et al. (2019) conducted a meta-analysis of ES in patients with isolated NDDs and NDDs plus associated conditions (e.g., syndromic features, systemic findings, neurologic features). Based on 30 studies comprising 3350 patients, the diagnostic yield of ES (31% in isolated NDD, 53% in NDD plus associated conditions, and 36% overall) was substantially higher than the generally accepted diagnostic yield of CMA (10%–20%). Srivastava et al. (2019) proposed a tiered workup beginning with ES and followed by CMA as second tier if ES analysis did not include CNV detection (Pfundt et al. 2017); if still no diagnosis, the investigators suggested additional tests to consider as indicated based on clinical presentation.

Some important genetic disorders are still not readily detected by NGS techniques, such as trinucleotide repeat expansions in fragile X syndrome and methylation defects in a subset of cases of Angelman syndrome (Biesecker and Green 2014); therefore, careful phenotyping and thoughtful consideration of a differential diagnosis are still crucial. Nonetheless, with decreasing cost and the superior diagnostic yield, in the future ES/GS will likely become the first-tier test for patients with suspected monogenic disorders including NDDs.

GENETIC COUNSELING FOR NDDs TO PROMOTE DECISION-MAKING AND ADAPTATION

Every family who has a child diagnosed with an NDD has unique expectations and interest in pursuing a genetic evaluation. Thus, genetic counseling entails understanding what these expectations and interests are and how they originated. Addressing them directly can lead to providing an invaluable service to enable patients and their families to understand the contribution of genetics to an individual's diagnosis of NDD and to make informed decisions about testing and management. In addition, even for families who elect not to pursue testing, genetic counseling can still be beneficial to help them understand the role of genetics in NDDs, cope with the challenges surrounding NDDs, and adapt to their child's disability.

Parental Attitudes toward Diagnosis

Parents have many reactions after their child has been diagnosed with an NDD. They often experience acute grief and sorrow over the loss of the hoped-for child, as well as the loss of their expected future (Bruce et al. 1996; Nelson Goff et al. 2013). Parents are faced with the prospect

of caring for a child through adulthood who may never be able to live independently. Parents worry about the impact on their day-to-day life and finances, as well as impact on their other typically developing children (Schuntermann 2007). Receiving an NDD diagnosis brings with it anxiety and uncertainty about the future (Makela et al. 2009). Parents frequently experience social isolation and stigmatization (Ali et al. 2012). They grapple with the question of why this has happened to them and their child, and this often triggers feeling of guilt and blame (Ali et al. 2012). Parents may also worry about the possibility of subsequent children having an NDD and/or if they did something to have caused the diagnosis to occur in their child. All of this naturally leads to a search for an explanation.

In a qualitative study of parents of children with unidentified multiple congenital anomaly syndromes, Rosenthal et al. (2001) defined dimensions to parents' views on the importance of diagnostic information: labeling (e.g., to help other people understand their child's condition), causation, prognosis, treatment, acceptance, and social support. Prognosis included wanting to know future health risks, mortality, how much progress their child is expected to make, and boundaries of their child's capabilities. Similarly, in a qualitative study of parents of children with and without a diagnosis for their child's ID, Makela et al. (2009) found that parents' interest in a diagnosis stemmed from seeking validation, information to guide expectations and treatment, assistance with accessing services, social support, and satisfying their curiosity.

The drive to find a diagnosis and etiology may be intense in close proximity to the time when an NDD diagnosis is made, especially for parents of younger children (Rosenthal et al. 2001; Makela et al. 2009). This drive may lessen somewhat as the child ages and parents have adapted to their child's condition over time. However, when given the opportunity, many parents of older children remain interested in finding the cause of their child's NDD. Renewed interest in a diagnosis and etiology may be triggered by learning of advances in genetic testing or prompting by typically developing siblings who are approaching adulthood and facing reproductive decisions, among other reasons.

Exploring the Relationship between Genetics and NDDs

After a child has been diagnosed with an NDD, it may not be intuitive to parents when their child's health-care provider raises the issue of genetics. For example, parents may ask questions like "My child has autism, what do you mean he/she could have a genetic problem?" and "So, if you diagnose a genetic disorder, does that mean my child doesn't have autism?" They may not realize that genetic variation has been implicated in NDDs and, instead, have other suspicions as to its etiology. Often parents attribute their child's NDD to a concrete event or tangible factor, such as nuchal cord at birth or maternal stress during pregnancy. The genetic counselor should respectfully explore these suspicions to understand and appreciate what use they serve, and only when needed, correct misconceptions with information supported by the medical literature. Research has shown that parents accept multiple attributions for their child's condition (Dong 2005; Vetsch et al. 2019). As such, they can accept a spiritual cause alongside a biological one.

When broaching the topic of genetics, it can be helpful to distinguish the NDD diagnosis from the potential etiologic diagnosis. For example, the genetic counselor can explain that NDD diagnoses such as ID and ASD describe the developmental concern, which stems from differences in brain functioning; genes influence how a person's brain develops and functions, so changes in genes (a genetic disorder) may result in differences in brain functioning, which leads to the symptoms that are labeled with an NDD diagnosis. By introducing the concept of multifactorial causes, this acknowledges that other factors including the environment may contribute to the complexities seen in NDDs. In our experience, separating these out—cause of brain difference (etiology) leading to NDD diagnosis—may help parents understand the

role of genetics and why genetic evaluation and testing are being offered. Making this distinction may also help parents understand why establishing a specific genetic diagnosis usually does not change their child's NDD diagnosis.

Facilitating Decision-Making about Genetic Testing

Much of the treatment for NDDs, such as therapies and educational supports, is aimed at maximizing developmental potential and managing symptoms irrespective of etiology. Yet, it can also be important for the individual's care and to the family to determine the underlying cause. Establishing a specific genetic diagnosis may impact an individual's medical management and treatment, allow provision of prognostic information, enable family counseling with a specific recurrence risk, and reproductive options, as well result in psychological and social benefits to the individual and the family. On the other hand, there are important limitations of genetic testing and potential risks. Although genetic testing is a standard recommendation in the evaluation of patients with an NDD, it is ultimately a choice made by the family and, therefore, the genetic counselor must present a balanced discussion of potential benefits, limitations, and possible downsides of genetic testing (Cohen et al. 2013). Key benefits, limitations, and risks of genetic testing in NDD are summarized in Box 2 and described below.

Regarding the potential benefits of genetic testing in NDD, identifying a genetic etiology for an NDD through genetic testing may offer an end to a diagnostic odyssey and provide closure by ruling out other causes, as well as provide a "name" that unifies the individual's symptoms and challenges (Rosenthal et al. 2001). A genetic diagnosis may also direct medical management by providing information about other associated medical problems or possible future complications that need to be evaluated, supporting

BOX 2. KEY BENEFITS, RISKS, AND LIMITATIONS OF GENETIC TESTING IN NDDs

Potential benefits

- End diagnostic odyssey
- Provide a name that unifies child's symptoms
- Enable provision of prognostic information
- Enable tailoring of medical management
- Result in targeted treatment
- Alleviation of negative emotions such as guilt or blame
- Increase access to services and condition-specific support groups
- Enable counseling with specific recurrence risk and reproductive options

Potential risks and limitations

- Failure to identify definitive etiologic diagnosis
- Genetic diagnosis may not alter medical management or treatment
- Genetic diagnosis associated with limited or no prognostic information
- Possibility of variants of unknown significance, incidental/secondary findings, or unexpected information about familial relationships
- Negative emotional responses to results
- Unexpected diagnosis of parent or relative based on inherited variant
- Concerns about genetic discrimination and privacy of data

evidence for early intervention and educational supports, and using prognostic information in order to better prepare a family for their child's future. When discussing the benefit of learning prognostic information, it is important to advise families that the genetic result may not be fully predictive of future (dis)ability because there is often variability in outcomes. Furthermore, even for well-described conditions, there can be limited information available on outcomes in adulthood. Rarely, a targeted treatment is available, although this may change over time with advances in research. Knowledge of inheritance may alleviate feelings of guilt or blame for parents if the causative variant occurred de novo and enable specific recurrence risk counseling and family planning options as discussed below.

On the other hand, there are several reasons a family may decline genetic testing. First, there is no guarantee that genetic testing will identify the etiologic diagnosis. For GDD/ID, currently genetic testing identifies the cause about half of the time, taking into account the ∼10% yield of CMA and ∼40% yield of ES, and the yield is substantially lower for isolated ASD without comorbidities (Lee et al. 2014a; Srivastava et al. 2014, 2019; Kuperberg et al. 2016; Nolan and Carlson 2016; Clark et al. 2018; Wright et al. 2018). The possibility of uncovering variants of unknown significance (VUSs) may be a deterrent to some families, as a VUS could trigger worry and/or frustration due to lack of definitive information to interpret the pathogenicity of the variant. Similarly, identification of a genetic etiology may not result in immediate changes to medical management or prognosis. As a result, some families may defer testing in the hope that technology and knowledge will improve over time, reduce the likelihood of learning uncertain results, and increase the probability of learning medically useful information. Parents also consider the potential emotional impact of results, such as fear that they will learn that one or both parents "caused" their child's condition in the case of an inherited disorder. Additionally, because NDD represents a spectrum of DBD, identification of an inherited genetic variant in a family may suggest the presence of related diagnoses in family members. Genetic testing may also reveal unexpected familial relationships such as consanguinity or misattributed parentage. Finally, some families are concerned about genetic discrimination and privacy of genetic data because of the limitations of the Genetic Information Nondiscrimination Act and other legislation, especially as they make plans for long-term care for their child.

Counseling about Recurrence Risk for NDDs

One of the major motivators for families to pursue genetic testing is knowledge of a specific recurrence risk (Finucane and Myers 2016). Many parents express great fear about the possibility of the condition happening again in their future children and concern about the potential risks to other family members, thus creating the desire for accurate recurrence risk counseling. Frequently, in cases in which the family history is negative, genetic disorders that present with NDD are due to de novo variants (Gilissen et al. 2014), which are associated with low recurrence risk for future siblings. On the other hand, autosomal dominant, autosomal recessive, and X-linked disorders are associated with substantially higher recurrence risks. Identifying a specific genetic diagnosis and determining the respective inheritance pattern allows for counseling with a specific risk figure and enables the use of reproductive testing options. This outcome may be realized by family members, as well as by individuals with milder NDDs who may have children of their own in the future. For siblings and other at-risk relatives, targeted testing for a causal variant may allow for diagnosis and early intervention. It is important to emphasize in the case of an inherited disorder, there is nothing the parent(s) did that caused the condition and to help them appreciate that they had no control over its occurrence.

In the absence of an identifiable genetic etiology, empiric recurrence risk estimates are used. There are several limitations in using empiric recurrence risks for NDDs. Over time, diagnostic criteria for certain NDDs change and study populations may be limited in size, com-

promising the accuracy of the risk estimates. In certain clinical scenarios, these estimates may not effectively account for the possibility of an affected parent, as variable expressivity and comorbidities can be present in NDDs, which suggests a higher recurrence risk. The 2013 ACMG guidelines (Schaefer et al. 2013) stated that the accepted recurrence risk for full siblings of a child with ASD is in the range of 3% to 10%. More recently, larger studies have been published to update and refine empiric risks that take into account new diagnostic criteria and advances in genetic testing (Ozonoff et al. 2011). As reviewed by Schaefer (2016), it is now recommended to provide a 10%–20% recurrence risk for full siblings of a child with ASD and a 30%–50% risk if there is more than one affected sibling. Empiric recurrence risk for a full sibling of a child with ID is ~3% and increases to 10% if a parent is also diagnosed with ID (Harper 2010). Genetic counselors have an especially important role in helping parents make informed family planning decisions and cope with the fear of recurrence when there is not a single definitive probability of recurrence.

Delivering the Genetic Diagnosis

Genetic counselors play a key role in delivery of a genetic diagnosis. Although the experience of receiving a genetic diagnosis is usually difficult for parents, research has shown that how the diagnosis is delivered impacts whether the experience is perceived by parents as positive or negative (Nelson Goff et al. 2013; Waxler et al. 2013; Ashtiani et al. 2014).

Genetic counselors should be cognizant of how recently the parents received their child's NDD diagnosis. Parents of children who were recently diagnosed with an NDD may still be coming to terms with the practical and emotional ramifications of their child's developmental disability and experiencing acute grief, so receiving a genetic diagnosis could be further overwhelming or possibly devastating. In contrast, parents of children who are older or have had a long-standing NDD diagnosis may be better adapted to their child's disability and capabilities, so they may have a more positive experience of receiving the diagnosis and may experience a sense of relief (Waxler et al. 2013).

Two studies specifically examined parental experiences of receiving a genetic diagnosis for their child's NDD, and the findings were remarkably consistent (Waxler et al. 2013; Ashtiani et al. 2014). Themes that emerged from these studies included the importance of communicating hope, emotional support, up-to-date information (verbal and written), resources, and follow-up plans. In addition, both studies underscored the importance of engaging parents in a discussion during which their emotions, questions, and concerns are elicited and addressed. Box 3 summarizes suggestions for delivery of a genetic diagnosis in NDD based on these studies.

Managing Uncertainty and Increasing Parental Sense of Control

Adaptation can be defined as the dynamic and multidimensional process of coming to terms with the implications of a health threat and the observable outcomes of that process (Biesecker and Erby 2008). As reviewed by these investigators, the appraisals individuals make in response to a health threat (in this context, parenting a child with an NDD), such as perceived uncertainty and personal control, are important predictors of adaptation to living with a genetic condition or risk.

It can be disappointing and frustrating to families when all available genetic testing fails to identify an etiologic diagnosis. The uncertainty generated by the absence of a diagnosis may lead to lower perceived personal control and less optimism (Madeo et al. 2012). Even when a genetic etiology is identified, there remain levels of uncertainty for medical management and prognosis, particularly for rare conditions and those with substantial phenotypic variability (Han et al. 2017), and parents may perceive a low sense of control (Lipinski et al. 2006). Uncertainty may be appraised by parents as negative/bad or positive/good (Whitmarsh et al. 2007). As an example of the latter, some parents may feel that "an uncertain outcome leaves open the possibilities for

BOX 3. SUGGESTIONS FOR DELIVERY OF A GENETIC DIAGNOSIS IN NDDs

- Attend to parents' emotions and provide emotional support
- Offer messages of hope and perspective.
- Engage the parents in a dialogue and encourage parents to talk (avoid verbal dominance).
- Check in with parents throughout the discussion and reengage as necessary.
- Limit the use of difficult medical terminology.
- Elicit parental preferences (e.g., asking whether they would like to see a picture of other individuals with the same condition).
- Provide the most up-to-date information possible.
- Provide balanced information (e.g., in addition to describing the features of the condition, point out aspects of the child's health that are not expected to be affected, if appropriate).
- Give written information about the diagnosis and an outline of follow-up plans.
- Give resources such as condition-specific support groups, when available.

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a positive outcome in their child" (Madeo et al. 2012). Depending on parental appraisal, perceived uncertainty could aid or impede parental adaptation.

For parents struggling with uncertainty, genetic counselors can help by providing pieces of relatively certain information. For example, when appropriate, the parents can be told that the child's condition is not expected to be degenerative or life-limiting, other medical complications are not anticipated, and the child will still benefit from therapies. It may also be helpful to reassure parents that all available testing has been pursued and an exhaustive search for information has been performed, and then the genetic counselor can assist them with coping with the residual uncertainty, stress, and related challenges of caring for their child with NDD. Genetic counselors can use interventions that aid parents in using more effective coping strategies (e.g., Haakonsen Smith et al. 2018). To enhance parents' sense of personal control, genetic counselors can help parents recognize aspects of their situation over which they do have control (e.g., making decisions about therapies and other treatments) and identify tangible ways they may be able to gain some control (e.g., joining a support group, advocating for research into the condition).

Fostering Hope and Meaning-Making

As discussed above, messages of hope are important to share with parents during the process of delivering a genetic diagnosis. In addition, research has shown a relationship between hope, uncertainty, and psychological adaptation. Hope can be conceptualized as a cognitive process that is comprised of a sense of agency (goal-directed determination) and pathways (planning of ways to meet goals) (Snyder et al. 1991). In a study of caregivers of children with Down syndrome, hope and perceived uncertainty were significantly associated with caregiver adaptation (Truitt et al. 2012). Based on their findings, the investigators proposed that genetic counselors can explore what parents are hoping for and evaluate the degree to which that is adaptive. In addition, genetic counselors can help parents identify new opportunities and ways to work toward those goals as well as reinforce the steps parents are already taking.

Meaning-making is a key component of the adaptation process. In a study of family caregivers of individuals with developmental disabilities, Werner and Shulman (2013) found that identifying positive meaning in caregiving was a strong predictor of caregivers' subjective well-being. Genetic counselors can facilitate a

discussion with parents about their experience of being a caregiver and encourage them to tell their story, verbally or through a writing exercise. This allows parents an opportunity for "cognitive restructuring" that may help develop a sense of meaning and also may help them integrate the genetic/biological explanation for their child's NDD with other causal beliefs (Biesecker and Erby 2008).

Addressing Stigma, Shame, and Guilt

Parents of children with NDDs frequently experience affiliate stigma, defined as the internalized stigma experienced by an unaffected individual, because of his or her association with a person who bears a stigma (an NDD in this case), and affiliate stigma may have a negative impact on their well-being (Ali et al. 2012). Feelings of shame and guilt are also common and may be associated with poor psychological outcomes for parents such as anxiety and depression (Gallagher et al. 2008; Ali et al. 2012). Parental self-esteem and social support are further predictors of well-being and may protect against the negative effects of affiliate stigma (Werner and Shulman 2013). Genetic counselors can explore with parents their experience with stigma, the ways in which they currently cope, and the extent to which those strategies are effective. Genetic counselors can also assess the parent's social support network. All parents should be referred to relevant support groups, although some parents may need additional professional support or long-term counseling.

Finding Opportunities for Social Support

Genetic counselors can help families with NDDs by connecting them with resources and support groups. The ability to connect with support groups and research organizations is helpful as there are other individuals who understand their unique situation. There are multiple organizations dedicated to genetic disorders with NDD such as Unique (rarechromo.org), MyGene2 (mygene2.org), Genome Connect (genomeconnect.org), and Simons Searchlight (simonsearchlight.org). Even for rare conditions for which there may not be an established foundation, the approachability and ease of social media allows for small groups to form that can grow in size, as more individuals pursue genetic testing and are identified with the same diagnosis (Rocha et al. 2018). The growth of these groups can provide research opportunities into specific treatments and natural history studies as a potential study population is easily accessible. For individuals who do not have a known genetic diagnosis, there are a number of general support organizations centered on the NDD diagnosis, such as The Arc (thearc.org) and Autism Speaks (autismspeaks.org).

CONCLUDING REMARKS

We are on the cusp of precision medicine for individuals with NDDs. ID and related disorders have always been considered incurable, with treatment instead focused on symptom management and therapies to support development. Genomic advances have led to an increased understanding of the pathophysiology and neurobiology of NDDs, and it is expected that this will eventually lead to targeted treatments based on underlying genetic etiology. There are more than 80 NDD-associated IEMs that have established treatments (Sayson et al. 2015). Moreover, efforts are underway to develop novel therapeutics for genetic conditions with NDDs. For example, everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is used for treatment of tumor manifestations in patients with tuberous sclerosis complex. Impressively, emerging evidence suggests that this drug is also beneficial for controlling seizures and improving neuropsychiatric symptoms (Kilincaslan et al. 2017). As another example, in a mouse model of Kabuki syndrome, postnatal treatment with a histone deacetylase inhibitor improved neurogenesis and ameliorated functional deficits (Bjornsson et al. 2014). This shows great promise for treatment of ID in Mendelian disorders of the epigenetic machinery and potentially other related conditions in the future. The vast potential for targeted treatment is perhaps the strongest impetus for genetic evaluation and testing in individuals with NDDs.

Genetic counselors are now poised to take a prominent role in the field of neurodevelopmental medicine. Similar to specialties such as oncology and cardiology in which genetic counselors provide services outside of the traditional medical genetics clinic, genetic counselors can create and develop their own positions in pediatric neurology and developmental pediatrics clinics. By partnering our genetics knowledge and counseling skills with the clinical expertise of these specialists, we can greatly increase access to genetic evaluation and testing for individuals with NDD. Finally, although further evidence is needed from studies of interventions in this population, research thus far has identified potential targets for genetic counseling to facilitate adaptation among parents of individuals with NDDs.

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REFERENCES

Ali A, Hassiotis A, Strydom A, King M. 2012. Self stigma in people with intellectual disabilities and courtesy stigma in family carers: a systematic review. *Res Dev Disabil* **33:** 2122–2140. doi:10.1016/j.ridd.2012.06.013

Al-Nabhani M, Al-Rashdi S, Al-Murshedi F, Al-Kindi A, Al-Thihli K, Al-Saegh A, Al-Futaisi A, Al-Mamari W, Zadjali F, Al-Maawali A. 2018. Reanalysis of exome sequencing data of intellectual disability samples: yields and benefits. *Clin Genet* **94:** 495–501. doi:10.1111/cge.13438

American Psychiatric Association. 2013. *Diagnostic and statistical manual of mental disorders*, 5th ed. American Psychiatric Association, Arlington, VA.

Ashtiani S, Makela N, Carrion P, Austin J. 2014. Parents' experiences of receiving their child's genetic diagnosis: a qualitative study to inform clinical genetics practice. *Am J Med Genet A* **164:** 1496–1502. doi:10.1002/ajmg.a.36525

Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Kurzius-Spencer M, Zahorodny W, Robinson Rosenberg C, White T, et al. 2018. Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. *MMWR Surveill Summ* **67:** 1–23. doi:10.15585/mmwr.ss6706a1

Biesecker BB, Erby L. 2008. Adaptation to living with a genetic condition or risk: a mini-review. *Clin Genet* **74:** 401–407. doi:10.1111/j.1399-0004.2008.01088.x

Biesecker LG, Green RC. 2014. Diagnostic clinical genome and exome sequencing. *N Engl J Med* **370:** 2418–2425. doi:10.1056/NEJMra1312543

Bjornsson HT, Benjamin JS, Zhang L, Weissman J, Gerber EE, Chen Y-C, Vaurio RG, Potter MC, Hansen KD, Dietz HC. 2014. Histone deacetylase inhibition rescues structural and functional brain deficits in a mouse model of Kabuki syndrome. *Sci Transl Med* **6:** 256ra135. doi:10.1126/scitranslmed.3009278

Bruce EJ, Schultz CL, Smyrnios KX. 1996. A longitudinal study of the grief of mothers and fathers of children with intellectual disability. *Br J Med Psychol* **69:** 33–45. doi:10.1111/j.2044-8341.1996.tb01848.x

Chaste P, Leboyer M. 2012. Autism risk factors: genes, environment, and gene–environment interactions. *Dialogues Clin Neurosci* **14:** 281–292.

Clark MM, Stark Z, Farnaes L, Tan TY, White SM, Dimmock D, Kingsmore SF. 2018. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med* **3:** 16. doi:10.1038/s41525-018-0053-8

Cohen J, Hoon A, Wilms Floet AM. 2013. Providing family guidance in rapidly shifting sand: informed consent for genetic testing. *Dev Med Child Neurol* **55:** 766–768.

Dashnow H, Lek M, Phipson B, Halman A, Sadedin S, Lonsdale A, Davis M, Lamont P, Clayton JS, Laing NG, et al. 2018. STRetch: detecting and discovering pathogenic short tandem repeat expansions. *Genome Biol* **19:** 121. doi:10.1186/s13059-018-1505-2

DeStefano F, Price CS, Weintraub ES. 2013. Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *J Pediatr* **163:** 561–567. doi:10.1016/j.jpeds.2013.02.001

Dong DA. 2005. "Causal attributions for autistic spectrum disorders: influences on perceived personal control." MS Thesis, Bloomberg School of Public Health of Johns Hopkins University, Baltimore.

Finucane B, Myers SM. 2016. Genetic counseling for autism spectrum disorder in an evolving theoretical landscape. *Curr Genet Med Rep* **4:** 147–153. doi:10.1007/s40142-016-0099-9

Gallagher S, Phillips AC, Oliver C, Carroll D. 2008. Predictors of psychological morbidity in parents of children with intellectual disabilities. *J Pediatr Psychol* **33:** 1129–1136. doi:10.1093/jpepsy/jsn040

Gentner MB, Leppert MLO. 2019. Environmental influences on health and development: nutrition, substance exposure, and adverse childhood experiences. *Dev Med Child Neurol* **61:** 1008–1014. doi:10.1111/dmcn.14149

Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BWM, Willemsen MH, Kwint M, Janssen IM, Hoischen A, Schenck A, et al. 2014. Genome sequencing identifies major causes of severe intellectual disability. *Nature* **511:** 344–347. doi:10.1038/nature13394

Haakonsen Smith C, Turbitt E, Muschelli J, Leonard L, Lewis KL, Freedman B, Muratori M, Biesecker BB. 2018. Feasibility of coping effectiveness training for caregivers of children with autism spectrum disorder: a

genetic counseling intervention. *J Genet Couns* **27:** 252–262. doi:10.1007/s10897-017-0144-1

Han PKJ, Umstead KL, Bernhardt BA, Green RC, Joffe S, Koenig B, Krantz I, Waterston LB, Biesecker LG, Biesecker BB. 2017. A taxonomy of medical uncertainties in clinical genome sequencing. *Genet Med* **19:** 918–925. doi:10.1038/gim.2016.212

Harper PS. 2010. *Practical genetic counselling*, 7th ed. CRC Press, Boca Raton, FL.

Hehir-Kwa JY, Pfundt R, Veltman JA. 2015. Exome sequencing and whole genome sequencing for the detection of copy number variation. *Expert Rev Mol Diagn* **15:** 1023–1032. doi:10.1586/14737159.2015.1053467

Ho K, Wassman E, Baxter A, Hensel C, Martin M, Prasad A, Twede H, Vanzo R, Butler M. 2016. Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders using an ultra-high resolution chromosomal microarray optimized for neurodevelopmental disorders. *Int J Mol Sci* **17:** 2070. doi:10.3390/ijms.17122070

Kilincaslan A, Kok BE, Tekturk P, Yalcinkaya C, Ozkara C, Yapici Z. 2017. Beneficial effects of everolimus on autism and attention-deficit/hyperactivity disorder symptoms in a group of patients with tuberous sclerosis complex. *J Child Adolesc Psychopharmacol* **27:** 383–388. doi:10.1089/cap.2016.0100

Kuperberg M, Lev D, Blumkin L, Zerem A, Ginsberg M, Linder I, Carmi N, Kivity S, Lerman-Sagie T, Leshinsky-Silver E. 2016. Utility of whole exome sequencing for genetic diagnosis of previously undiagnosed pediatric neurology patients. *J Child Neurol* **31:** 1534–1539. doi:10.1177/0883073816664836

Lee H, Deignan JL, Dorrani N, Strom SP, Kantarci S, Quintero-Rivera F, Das K, Toy T, Harry B, Yourshaw M, et al. 2014a. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA* **312:** 1880–1887. doi:10.1001/jama.2014.14604

Lee RW, Poretti A, Cohen JS, Levey E, Gwynn H, Johnston MV, Hoon AH, Fatemi A. 2014b. A diagnostic approach for cerebral palsy in the genomic era. *Neuromolecular Med* **16:** 821–844. doi:10.1007/s12017-014-8331-9

Lipinski SE, Lipinski MJ, Biesecker LG, Biesecker BB. 2006. Uncertainty and perceived personal control among parents of children with rare chromosome conditions: the role of genetic counseling. *Am J Med Genet C Semin Med Genet* **142C:** 232–240. doi:10.1002/ajmg.c.30107

Madeo AC, O'Brien KE, Bernhardt BA, Biesecker BB. 2012. Factors associated with perceived uncertainty among parents of children with undiagnosed medical conditions. *Am J Med Genet A* **158A:** 1877–1884. doi:10.1002/ajmg.a.35425

Makela NL, Birch PH, Friedman JM, Marra CA. 2009. Parental perceived value of a diagnosis for intellectual disability (ID): a qualitative comparison of families with and without a diagnosis for their child's ID. *Am J Med Genet A* **149A:** 2393–2402. doi:10.1002/ajmg.a.33050

Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, et al. 2010. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* **86:** 749–764. doi:10.1016/j.ajhg.2010.04.006

Moeschler JB, Shevell M; Committee on Genetics. 2014. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics* **134:** e903–e918. doi:10.1542/peds.2014-1839

Monroe GR, Frederix GW, Savelberg SMC, de Vries TI, Duran KJ, van der Smagt JJ, Terhal PA, van Hasselt PM, Kroes HY, Verhoeven-Duif NM, et al. 2016. Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability. *Genet Med* **18:** 949–956. doi:10.1038/gim.2015.200

Moreno-De-Luca A, Myers SM, Challman TD, Moreno-De-Luca D, Evans DW, Ledbetter DH. 2013. Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. *Lancet Neurol* **12:** 406–414. doi:10.1016/S1474-4422(13)70011-5

Nelson Goff BS, Springer N, Foote LC, Frantz C, Peak M, Tracy C, Veh T, Bentley GE, Cross KA. 2013. Receiving the initial Down syndrome diagnosis: a comparison of prenatal and postnatal parent group experiences. *Intellect Dev Disabil* **51:** 446–457. doi:10.1352/1934-9556-51.6.446

Nolan D, Carlson M. 2016. Whole exome sequencing in pediatric neurology patients: clinical implications and estimated cost analysis. *J Child Neurol* **31:** 887–894. doi:10.1177/0883073815627880

Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Bryson S, Carver LJ, Constantino JN, Dobkins K, et al. 2011. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics* **128:** e488–e495.

Pfundt R, Del Rosario M, Vissers LELM, Kwint MP, Janssen IM, de Leeuw N, Yntema HG, Nelen MR, Lugtenberg D, Kamsteeg EJ, et al. 2017. Detection of clinically relevant copy-number variants by exome sequencing in a large cohort of genetic disorders. *Genet Med* **19:** 667–675. doi:10.1038/gim.2016.163

Rocha HM, Savatt JM, Riggs ER, Wagner JK, Faucett WA, Martin CL. 2018. Incorporating social media into your support tool box: points to consider from genetics-based communities. *J Genet Couns* **27:** 470–480. doi:10.1007/s10897-017-0170-z

Rosenthal ET, Biesecker LG, Biesecker BB. 2001. Parental attitudes toward a diagnosis in children with unidentified multiple congenital anomaly syndromes. *Am J Med Genet* **103:** 106–114. doi:10.1002/ajmg.1527

Sayson B, Popurs MAM, Lafek M, Berkow R, Stockler-Ipsiroglu S, van Karnebeek CDM. 2015. Retrospective analysis supports algorithm as efficient diagnostic approach to treatable intellectual developmental disabilities. *Mol Genet Metab* **115:** 1–9. doi:10.1016/j.ymgme.2015.03.001

Schaefer GB. 2016. Clinical genetic aspects of autism spectrum disorders. *Int J Mol Sci* **17:** 180. doi:10.3390/ijms17020180

Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. 2013. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med* **15:** 399–407. doi:10.1038/gim.2013.32

Schalock RL, Luckasson RA, Shogren KA, Borthwick-Duffy S, Bradley V, Buntinx WH, Coulter DL, Craig EM, Gomez SC, Lachapelle Y, et al. 2007. The renaming of "mental retardation": understanding the change to the term "intellectual disability". *Intellect Dev Disabil* **45:** 116–124. doi:10.1352/1934-9556(2007)45[116:TROMRU]2.0.CO;2

Schuntermann P. 2007. The sibling experience: growing up with a child who has pervasive developmental disorder or mental retardation. *Harv Rev Psychiatry* **15:** 93–108. doi:10.1080/10673220701432188

Siu MT, Weksberg R. 2017. Epigenetics of autism spectrum disorder. *Adv Exp Med Biol* **978:** 63–90. doi:10.1007/978-3-319-53889-1_4

Snyder CR, Harris C, Anderson JR, Holleran SA, Irving LM, Sigmon ST, Yoshinobu L, Gibb J, Langelle C, Harney P. 1991. The will and the ways: development and validation of an individual-differences measure of hope. *J Pers Soc Psychol* **60:** 570–585. doi:10.1037/0022-3514.60.4.570

Srivastava S, Cohen JS, Vernon H, Barañano K, McClellan R, Jamal L, Naidu S, Fatemi A. 2014. Clinical whole exome sequencing in child neurology practice. *Ann Neurol* **76:** 473–483. doi:10.1002/ana.24251

Srivastava S, Love-Nichols J, Dies K, Ledbetter D, Martin C, Chung W, Firth H, Frazier T, Hansen R, Prock L, et al. 2019. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. *Genet Med* doi:10.1038/s41436-019-0554-6.

Stark Z, Schofield D, Alam K, Wilson W, Mupfeki N, Macciocca I, Shrestha R, White SM, Gaff C. 2017. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. *Genet Med* **19:** 867–874. doi:10.1038/gim.2016.221

Tammimies K, Marshall CR, Walker S, Kaur G, Thiruvahindrapuram B, Lionel AC, Yuen RKC, Uddin M, Roberts W, Weksberg R, et al. 2015. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. *JAMA* **314:** 895–903. doi:10.1001/jama.2015.10078

Truitt M, Biesecker B, Capone G, Bailey T, Erby L. 2012. The role of hope in adaptation to uncertainty: the experience of caregivers of children with Down syndrome. *Patient Educ Couns* **87:** 233–238. doi:10.1016/j.pec.2011.08.015

Van Karnebeek CDM, Shevell M, Zschocke J, Moeschler JB, Stockler S. 2014. The metabolic evaluation of the child with an intellectual developmental disorder: diagnostic algorithm for identification of treatable causes and new digital resource. *Mol Genet Metab* **111:** 428–438. doi:10.1016/j.ymgme.2014.01.011

Vetsch J, Wakefield CE, Doolan EL, Signorelli C, McGill BM, Moore L, Techakesari P, Pieters R, Patenaude AF, McCarthy M, et al. 2019. 'Why us?' Causal attributions of childhood cancer survivors, survivors' parents and community comparisons—a mixed methods analysis. *Acta Oncol* **58:** 209–217. doi:10.1080/0284186X.2018.1532600

Vissers LE, Gilissen C, Veltman JA, 2016. Genetic studies in intellectual disability and related disorders. *Nat Rev Genet* **17:** 9–18. doi:10.1038/nrg3999

Waxler JL, Cherniske EM, Dieter K, Herd P, Pober BR. 2013. Hearing from parents: the impact of receiving the diagnosis of Williams syndrome in their child. *Am J Med Genet A* **161:** 534–541. doi:10.1002/ajmg.a.35789

Wenger AM, Guturu H, Bernstein JA, Bejerano G. 2017. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. *Genet Med* **19:** 209–214. doi:10.1038/gim.2016.88

Werner S, Shulman C. 2013. Subjective well-being among family caregivers of individuals with developmental disabilities: the role of affiliate stigma and psychosocial moderating variables. *Res Dev Disabil* **34:** 4103–4114. doi:10.1016/j.ridd.2013.08.029

Whitmarsh I, Davis AM, Skinner D, Bailey DB Jr. 2007. A place for genetic uncertainty: parents valuing an unknown in the meaning of disease. *Soc Sci Med* **65:** 1082–1093. doi:10.1016/j.socscimed.2007.04.034

Wright CF, McRae JF, Clayton S, Gallone G, Aitken S, FitzGerald TW, Jones P, Prigmore E, Rajan D, Lord J, et al. 2018. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. *Genet Med* **20:** 1216–1223. doi:10.1038/gim.2017.246

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