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Diagnostic genetic testing for neurodevelopmental psychiatric disorders: Closing the gap between recommendation and clinical implementation

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Abstract

Advances in laboratory testing have significantly increased the detection of rare genetic etiologies of neurodevelopmental psychiatric disorders (NPD), particularly developmental delay / intellectual disability, autism spectrum disorder, and schizophrenia. Establishing a genetic diagnosis has important medical and personal utility for individuals with these conditions. Diagnostic genetic tests for NPD are clinically available but under-utilized outside of medical genetics settings. Without clear multidisciplinary consensus recommendations, active involvement of medical specialists working with NPD patients, and practical education and training, the implementation of genetic testing for NPD will continue to lag behind other areas of medicine. In the long-term, collaborative efforts to address educational, logistical, and workforce obstacles will improve patient care and pave the way for targeted, effective NPD treatments.

Keywords

neurodevelopmental; psychiatric; genetic disorders; diagnostic genetic testing; copy number variants; single nucleotide variants; Autism; Schizophrenia; developmental delay; intellectual disability; genetic counseling; implementation; child neurology; child psychiatry; developmental pediatrics; precision medicine; Genomics; genomic sequencing

Introduction

Advances in clinical laboratory testing have significantly increased our ability to detect rare genetic etiologies of developmental and psychiatric conditions, including developmental delay / intellectual disability (DD/ID), autism spectrum disorder (ASD) and schizophrenia (SCZ). These and other disorders, such as attention deficit and hyperactivity disorder (ADHD) and Tourette's disorder, show overlap in symptomatologies and frequently occur as co-morbid conditions. As such, they can be categorized under the broad umbrella of neurodevelopmental psychiatric disorders (NPD). While NPD refers to this full continuum of pediatric and adult brain disorders, our primary focus here is on DD/ID, ASD, and SCZ, as these NPD have the most compelling evidence in support of routine clinical genetic testing.

Various diagnostic genetic tests to identify the underlying etiologies of NPD have been clinically available for decades. Beginning with low resolution karyotypes as far back as the

1960s, and advancing through today's next generation sequencing technologies, these tests have been almost exclusively employed by a small cadre of medical geneticists, limiting their clinical reach in NPD populations. A major breakthrough in genetic diagnosis came with the introduction of chromosomal microarray analysis (CMA) in the early 2000s, allowing clinical identification of many submicroscopic copy number variants (CNVs) (i.e., microdeletions and microduplications) which had previously gone undetected [1,2]. Over a decade of experience with CMA has revealed dozens of pathogenic CNVs that confer large effects on brain function and cut across a broad range of clinical NPD [3–5]. These CNVs have primary neurodevelopmental and psychiatric manifestations but vary with regard to the presence of congenital anomalies and overt facial dysmorphism [6,7].

Currently, the clinical availability of exome sequencing (ES) has significantly increased the diagnostic yield of genetic testing [8–10]. ES detects rare, pathogenic sequence variations in the coding regions of the genome, allowing the diagnosis of single gene etiologies of NPD. Many commercial laboratories have now expanded their ES analyses to also detect CNVs, eliminating the need for separate CMA in most cases [11]. At the same time, the cost of ES has dropped dramatically, while coverage by health insurance plans in some countries has increased, particularly for pediatric developmental indications [12]. The result has been an exponential rise over the past decade in the number of known genetic etiologies of NPD. Several large research surveys have reported pathogenic copy number and single gene variants for a combined yield of at least 40% of DD/ID and 25% of ASD [9,13–15]. Emerging data from SCZ cohorts has identified CNVs in up to 8% and sequence variants in 1–2% [16–21], with higher percentages among SCZ subgroups having significant cognitive disabilities and/or congenital anomalies [22,23]. Further SCZ studies are required to confirm these associations at a level beyond chance expectations and will likely increase the diagnostic yield. The high prevalence of rare causative variants in DD/ID and ASD has been corroborated by data from years of clinical testing in medical genetics practice. By contrast, diagnostic testing for SCZ etiologies is rarely offered in clinical settings. While preliminary research suggests more modest diagnostic yields for CMA and ES in SCZ – pointing to a predominantly polygenic etiology - our understanding of the contributory role of rare genetic variants in this population is still evolving [24,25].

Diagnostic Genetic Testing for NPD in Clinical Practice

Studies of rare genetic NPD etiologies have confirmed extensive phenotypic variability, even within families. The 1q21.1 recurrent microdeletion, for example, may manifest as ASD in a child, bipolar disorder and epilepsy in her mother, and a variety of different cognitive and behavioral symptoms in the extended family [26]. These observations have called into question the biological validity of current clinical diagnostic approaches, given their lack of consistency with the shared underlying biology and dimensional nature of neuropsychiatric traits [27,28]. They also highlight the important family implications of genetic diagnosis [3,29] and the potential for new treatment discoveries through cross-disorder research strategies [30]. Against this dynamic backdrop of gene discovery and dimensional models of brain disorders, however, the adoption of widely available diagnostic testing by non-geneticist NPD specialists (e.g., psychiatrists, developmental pediatricians, neurologists) has been slow to take root [31–33]. Currently, clinical genetic testing for NPD remains almost

entirely focused on young children, mainly targeting DD/ID and/or ASD, and implemented through referral to medical genetics specialists. This contrasts with other areas of medicine, such as Cardiology and Oncology where diagnostic genetic testing is already well-integrated into routine clinical care [34,35].

Published consensus guidelines from various expert panels and professional societies are in place for NPD commonly encountered by pediatric and adult brain specialists. For example, ES, CMA, and fragile X analysis are recommended by several groups for the evaluation of children with DD/ID and ASD, regardless of the presence of physical anomalies [2,9,36–39]. Similar guidelines for adults with these disorders have been slower to emerge, although evidence is building in support of the clinical and personal utility of diagnostic testing beyond childhood [3,40,41]. In both pediatric and adult medicine, genetic testing recommendations for the same clinical disorder may vary, depending on the particular professional group cited, the recency of its review, and the strength and clarity of its published statement. For example, the *American College of Medical Genetics* (ACMG) has long recommended fragile X and CMA for the evaluation of all children with DD/ID and ASD [36,38]. ACMG has not yet issued similar guidance for ES [42], although a separate consensus statement by multiple expert groups strongly recommends ES as a first-tier clinical test, citing evidence for high diagnostic yields in DD/ID and ASD [9]. The United Kingdom-based *National Institute for Health and Care Excellence* advocates a more restricted, traditional approach to genetic testing, based on input from Medical Genetics and weighted on the presence of dysmorphic features and congenital anomalies [43]. Some individual research groups have urged genetic testing for patients with SCZ [22,40], given reports of clinically relevant CNVs in this population; however, recommendations from professional psychiatric organizations have been more tepid. Practice guidelines from the *American Psychiatric Association* mention “genetic testing” without further description in a table of “suggested assessments” for individuals with SCZ [44]. The *Canadian Psychiatry Association* endorses consideration of “genetic testing based on the history and physical examination of the patient, especially at the time of the first episode of psychosis” [45]. The *International Society of Psychiatric Genetics* suggests that diagnostic testing “may have value” for patients with DD/ID and ASD, while offering no specific recommendations on SCZ [46].

In principal, best practices in clinical care should be agnostic to reimbursement and access issues, yet short-term concerns about the regional availability of certain genetic tests can weaken guidance. Such reticence is reflected in vague position statements that fail to adequately inform clinical decision-making, and in some cases, inappropriately advise the continued use of outdated technologies, such as karyotyping [37]. The lack of consistent, cross-disciplinary recommendations has slowed clinical implementation of diagnostic genetic testing for NPD, making it difficult to assess its diagnostic yield and utility outside of a research context. At the same time, the absence of clinical testing data, particularly for SCZ, has hampered the development of consensus guidelines, which would in turn drive insurance reimbursement. As a result of this circular dilemma, genetic testing for SCZ has so far failed to gain traction toward widespread implementation outside of medical genetics settings.

Surveys of NPD specialists reveal that they rarely initiate diagnostic testing, even in patients with ASD or ID/DD where the recommendations are strongest [33]. This is confirmed in studies of patient experiences, including a recent finding that only 3% of children with ASD had undergone both fragile X testing and CMA [31]. Reported barriers to implementation include: clinicians' lack of training in medical genetics; a scarcity of genetic counselors to manage consenting, results disclosure, and family follow-up; uncertainty about which test to choose; and difficulty interpreting and explaining test results. Additional obstacles include concerns about insurance coverage, as well as skepticism about the clinical utility of genetic diagnosis. It appears that NPD specialists are largely aware of genetic testing recommendations but rarely implement them [33]. Those who do most often refer patients for Medical Genetics specialty appointments without directly ordering recommended laboratory testing (Figure 1). Given the long waiting lists and limited availability of medical geneticists, this continued reliance on inefficient referral practices greatly reduces the chance of testing follow-through by patients with NPD and their families. Psychiatry, Neurology, and Developmental Pediatrics currently trail other areas of specialty medicine in integrating genetic testing into patient care [34,35], despite relatively high diagnostic yields and robust evidence for clinical utility in NPD. This lag also has important downstream implications for NPD research, as advances in precision medicine hinge on the identification of rare genomic variants which, when paired with clinical correlation, can fuel treatment breakthroughs [47,48].

Closing the Implementation Gap

We propose here three practical steps to address the current obstacles in the way of a successful evidence-based implementation of genetic testing for NPD in the clinic (Table 1.):

1. Establishment of cross-disciplinary consensus recommendations

Starting with diagnostic genetic testing for DD/ID, ASD, and SCZ, efforts are needed to synthesize competing recommendations, guidelines, and position statements into a single authoritative source of clear, prescriptive guidance. Recommendations should encompass both children and adults with DD/ID, ASD and SCZ, regardless of whether these diagnoses present as the primary referral indication or an observed secondary comorbidity. Consistent expert opinion, regularly updated to reflect changing laboratory technologies and relevant NPD discoveries, should continually inform test selection, including the future clinical use of polygenic risk scores [24,49]. Ideally, a joint practice guideline authored by representatives from multiple professional societies and stakeholders would ensure broad cross-disciplinary dissemination to NPD medical care providers. As the professional discipline most often on the front lines of diagnostic laboratory testing, Medical Genetics is an obvious choice to lead such an initiative, in close collaboration with relevant clinical NPD groups. In the United States, there is precedent for such an approach in Oncology, where genetic testing and surveillance recommendations are consolidated under widely implemented guidelines of the National Comprehensive Cancer Network [50]. As a secondary benefit, the establishment of national testing recommendations for cancer informed US healthcare policy and insurance coverage efforts, areas that remain to be addressed for NPD.

2. Creation of streamlined clinical workflows that minimize the burden of genetic test ordering and follow-up

For busy clinicians unfamiliar with genetic test selection and ordering in the age of next generation sequencing, the prospect of directly handling this aspect of NPD care can seem daunting [32,33,51]. However, the traditional practice of simply referring patients to a medical geneticist is no longer an acceptable way to ensure that testing recommendations are followed, given the volume of eligible patients and the scarcity of medical genetics providers. Fortunately, genetic test selection for DD/ID and ASD is relatively straightforward, in most cases involving a tiered strategy of fragile X analysis reflexing, if negative, to ES with CNV detection on the same patient sample. Local practices may vary but should be made transparent and available to ordering NPD clinicians. CMA may be the diagnostic test of choice for SCZ, rather than ES, based on the current low yield of detectable sequence variants. In North America, commercial genetics laboratories typically employ genetic counselors who serve as a technical resource for ordering providers, ensuring appropriate test selection. DNA can now be reliably extracted for analysis from saliva or oral buccal samples in most cases, facilitating specimen collection and shipping. Many labs also provide solutions for some of the most time-consuming aspects of genetic testing, including full-service handling of insurance pre-authorization requirements and patient billing.

Aside from these logistical considerations, there are more nuanced aspects of the genetic testing process that NPD clinicians can efficiently manage through careful workflow planning in collaboration with a regional genetics group. For example, genetic testing has the potential to reveal unanticipated findings with implications beyond the original testing indication, including the discovery of sensitive information about family relationships (e.g., non-paternity), as well as medically-actionable secondary genomic findings [52]. For this reason, an informed consent process is recommended prior to testing to alert patients to the types of results that might be revealed, while offering options for limited disclosure of secondary findings. Obtaining consent for genetic testing does not have to be an onerous process [53,54] and with appropriate education can be efficiently carried out by NPD specialists themselves or delegated to trained office staff.

NPD clinicians may not feel adequately prepared to interpret genetic laboratory test reports and may be reluctant to take on responsibility for ordering an unfamiliar test [32]. By establishing a mutually beneficial shared workflow with regional genetics providers, test results can be efficiently triaged, with a Medical Genetics referral generated only for those patients with positive or ambiguous results, as illustrated in figure 1. Cross-disciplinary collaborations such as these can increase adherence to genetic testing recommendations while advancing clinicians' knowledge about rare NPD etiologies. In the long-term, positive outcomes related to genetically-informed medical care and patient satisfaction will further reinforce the value of clinical genetic testing in the eyes of NPD specialists.

3. Development of practical genetics education strategies for new NPD trainees and established clinicians

At present, many established and future NPD clinicians, particularly psychiatrists, lack the necessary training that would allow them to routinely consider genetic testing as part of their diagnostic armamentarium [55]. Given the evidence for an increasing proportion of NPD patients for whom a genetic etiology can be identified, and the clinical importance of elucidating this aspect of their diagnosis, the inclusion of basic genetic knowledge in the training curricula for NPD clinicians is both logical and necessary. The extent of information offered during training does not have to cover a deep understanding of genetic architecture or the technical workings of various genetic testing methods, but should be sufficient to provide the clinician with confidence to consider genetic testing as part of the diagnostic work-up in his or her own practice. At the very minimum, basic knowledge should include a broad understanding of the current evidence from genetic studies which provides the rationale for testing; the different genetic testing methods and their specific yields; which pros and cons of testing should be discussed with patients; the practical aspects of ordering genetic testing; how workflows are organized locally (see previous section), and how test results are interpreted and communicated with the family. Recently, Nurnberger et al. [55] have proposed an inventory of themes in genetics along with recommendations to include these as essential knowledge components in the training of psychiatrists.

Conclusions

While individually rare, genomic copy number and sequence variants collectively account for a significant proportion of DD/ID, ASD, and SCZ etiologies. Establishing an underlying genetic diagnosis has important medical and personal utility for individuals with these conditions, while also unlocking rare disorder research opportunities that will drive precision medicine breakthroughs in NPD treatment. Powerful diagnostic genetic tests for NPD are clinically available but currently under-utilized outside of medical genetics settings. Without clear multidisciplinary consensus recommendations, a collaborative workflow regarding genetic testing across the NPD and genetic disciplines, and educational strategies about genetic testing for future NPD clinicians, the implementation of diagnostic genetic testing will continue to lag behind other areas of medicine. In the long-term, collaborative efforts to address educational, logistical, and workforce obstacles will improve patient care and pave the way for targeted, effective NPD treatments.

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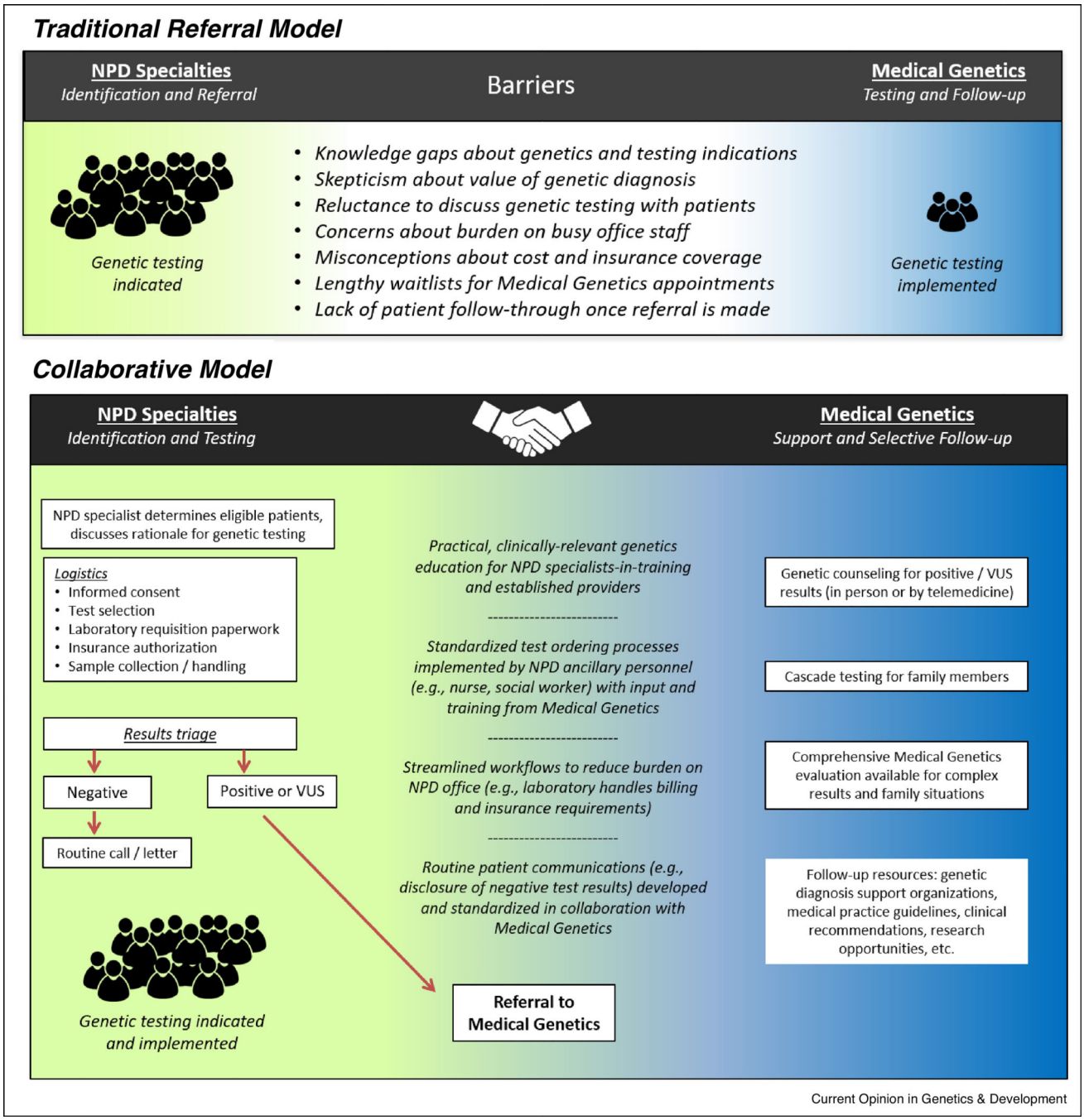

Fig. 1.

A traditional approach of referring patients to Medical Genetics is widely used by NPD clinicians but fails to achieve adequate implementation of genetic testing recommendations. A collaborative model facilitates consistent genetic testing and follow-up for patients with NPD and their families.

Table 1:

Strategies to Increase Implementation of Diagnostic Genetic Testing for NPD

Goal	Current Status	Proposed Strategy
Establishment of cross-disciplinary consensus recommendations on NPD genetic testing	• Competing and conflicting guidelines by multiple professional groups • Siloed dissemination and inconsistent compliance within NPD specialty areas	• Cross-disciplinary consensus and publication of a single, authoritative source of genetic testing guidance for children and adults with NPD • Regular updates to reflect changing laboratory technology and research evidence • Widespread dissemination across NPD clinical specialties and professional groups
Streamlined clinical workflows that minimize the burden of genetic test ordering and follow-up	• High administrative and logistical burden on NPD clinicians and office personnel • Low rates of implementation despite awareness of clinical recommendations • Reliance on traditional model of referral to Medical Genetics	• Collaboration and training from regional Medical Genetics resources on test selection, consent procedures, and results triage • NPD office staff and testing laboratory develop shared processes for billing, specimen collection, sample shipping, etc. • Standardized protocols for disclosure of negative results to patients, with positive and ambiguous results referred to Medical Genetics
Practical genetics education for trainees and established NPD clinicians	• Inconsistent knowledge base in medical genetics across NPD specialists • Need for NPD-specific training on test selection, diagnostic yields, results interpretation, and communication with patients and families	• Development of practical curricula for NPD trainees and established clinicians, with a focus on essential knowledge related to diagnostic genetic testing • Increased clinician confidence in genetic test implementation reinforced through training and illustrative positive experiences of patients diagnosed with genetic etiologies of NPD