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Survey of the Landscape of Society Practice Guidelines for Genetic Testing of Neurodevelopmental Disorders

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Abstract

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Author Contributions

All authors contributed to the conception and design of the study. SS and JJC performed the acquisition and analysis of the data. SS, JJC, and JSC drafted a significant portion of the manuscript or figures. All authors contributed significant intellectual content to the study and provided critical edits to the manuscript. Please see Supplementary Table 1 for a complete list of members of the IDDRC Workgroup on Advocating for Access to Genomic Testing.

Potential Conflicts of Interest

SS is on the Executive Committee of the American Academy of Pediatrics Council of Children with Council on Children with Disabilities (the American Academy of Pediatrics has published practice parameters referenced here). CAC is the President of the National Society of Genetic Counselors (which has published a practice parameter on epilepsy referenced here).

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Genetic testing of patients with neurodevelopmental disabilities (NDDs) is critical for diagnosis, medical management, and access to precision therapies. Because genetic testing approaches evolve rapidly, professional society practice guidelines serve an essential role in guiding clinical care; however, several challenges exist regarding the creation and equitable implementation of these guidelines. In this scoping review, we assessed the current state of United States professional societies' guidelines pertaining to genetic testing for unexplained global developmental delay, intellectual disability, autism spectrum disorder, and cerebral palsy. We describe several identified shortcomings and argue the need for a unified, frequently-updated and easily-accessible cross-specialty society guideline.

INTRODUCTION

Neurodevelopmental disorders (NDDs) or developmental disabilities are a spectrum of conditions characterized by delay, deviance, and/or dissociation across domains of childhood development (such as motor, problem solving, social-communication, and adaptive skills) [1]. NDDs are heterogeneous in clinical presentation, resulting in variable definitions. [2,3]. For the purposes of this manuscript, the term NDD will encompass global developmental delay (GDD), intellectual disability (ID), autism spectrum disorder (ASD), and cerebral palsy. We made this designation, because for each of these conditions, there are meta-analyses supporting the diagnostic utility of genetic testing among patients without a clearly identifiable acquired etiology [4–8]. Specifically, among individuals with GDD/ID and/or ASD, the prevalence of pathogenic chromosomal copy number variants (CNVs) and single nucleotide variants (SNVs)/small indels is approximately 10–15% and 30–40%, respectively [4,9]. For CP, the prevalence of pathogenic CNVs and SNV/small indels is approximately 5% and 20–30%, respectively [5,10].

With the expanding knowledge of genetic causes of NDDs and the rise of next-generation sequencing (NGS)[11], professional society guidelines pertaining to genetic testing are increasingly important in clinical care. These guidelines, or "practice parameters", are based on comprehensive evidence reviews to inform best practices with respect to diagnosis, management, and treatment [12]. Since the early 2000s, multiple guidelines for genetic testing for NDDs have been published by a variety of specialty organizations across neurology, pediatrics, genetics, and psychiatry. These guidelines have important clinical implications, as they are frequently referenced by clinicians when determining genetic testing utility/plans. Furthermore, payers use society guidelines when writing medical policies to determine insurance coverage for genetic testing for NDDs [13,14]. The quality, consistency, and accessibility of these guidelines thus has great influence on care outcomes for children with NDDs.

Despite the key role that society guidelines play in access to genetic testing for NDDs, a summary of recommendations across professional societies does not yet exist. Consistency between guidelines is important for several reasons. If there are differing recommendations for genetic testing for NDDs, insurance companies can deny coverage for one type of test over another, citing a specific guideline which supports their position. For example, in their policy dated January 1, 2024, United Health Care has stated it will approve GS/deem it

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medically necessary if “neither chromosome microarray analysis (CMA) nor WES have been performed” (https://www.uhcprovider.com/content/dam/provider/docs/public/policies/medicaid-comm-plan/whole-exome-whole-genome-sequencing-cs.pdf). Second, there can be confusion among patients if providers from one medical specialty suggest one type of etiological evaluation that differs from that of another medical specialty, which can perpetuate healthcare disparities. Third, there may suboptimal utilization of healthcare costs and resources (genetic counseling visits, physician visits), as well as undue patient burden (time, expense), if individuals undergo a set of genetic tests based on one guideline that has lower diagnostic yield and lower cost-effectiveness compared to another guideline. Therefore, we aimed to fill this gap by conducting a scoping review of the literature on available U.S.-based professional society practice guidelines that contain recommendations for genetic testing of unexplained NDDs. We describe the current practice guideline landscape, highlight challenges, and provide recommendations to improve the efficiency, contemporaneity, cohesiveness, and impact of societal guidelines for genetic testing for NDDs.

The target audience for this review are clinicians, policy makers, and medical societies across multiple medical disciplines, including pediatrics, developmental-behavioral pediatrics, psychiatry, genetics, and neurology. The ultimate goal is to spearhead the creation of unified, frequently updated, and easily accessible cross-specialty society guidelines.

METHODS: IDENTIFICATION OF RELEVANT PRACTICE GUIDELINES

We conducted a scoping review including a primary search strategy and manual article selection to identify practice guidelines. In the primary search strategy, we searched articles indexed by PubMed (title, abstract, and keyword search via https://pubmed.ncbi.nlm.nih.gov/) with the following query:

> (“global developmental delay” OR “intellectual disability” OR “autism” OR “cerebral palsy” OR “developmental disabilities”) AND (“practice parameter” OR “practice guideline” OR “evidence report” OR “clinical guideline” OR “consensus statement” OR “comprehensive evaluation” or “clinical report” or “practice resource”)

Notably, we did not include the term “genetic(s)” in the search query, as society guidelines focusing on multiple aspects of care related to a specific NDD may not include this term(s) in the abstract or as part of MeSH keywords identified by the PubMed search.

We applied inclusion/exclusion criteria to the resulting articles. Inclusion criteria were: statement by a U.S. medical organization/society, focus on an NDD (specifically GDD/ID, ASD, and/or CP), and inclusion of clinical recommendations pertaining to genetic testing. Exclusion criteria were: non-English article; erratum to another article; commentary article; animal, *in vitro*/*in vivo*, biomarker, or other biological study; case report/case series; primary research article; review article or guidelines related to a specific genetic disorder; focus on a study population not of interest; focus on outcomes, management, or diagnostic practices not of interest; lack of clinical recommendations; involvement by an organization outside of the U.S.; retired guideline (if there is explicit mention of it being retired in

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the full PDF text of the article or the source website of the article); guideline replaced by a more contemporary version from the same medical society focusing on the same target population; and guideline/review of guidelines without involvement of a professional organization. The manual article selection phase involved a direct query of all authors to identify any additional articles meeting inclusion/exclusion criteria.

For each article included in the review, we extracted the following data:

- Article metadata
- Society involved and its overall clinical focus
- NDD population of interest
- General focus of the guideline (etiology, diagnosis, management)
- Recommendations pertaining to genetic testing including choice of first-line test(s)
- Whether the guideline focused on a disorder (such as GDD/ID) or a genetic test (such as ES)

The first author SS manually completed the article search. Both first authors completed the record screening, eligibility review, and data collection. There were no missing data. This study did not require a registered research protocol or statement of approval by an ethical standards committee.

RESULTS: OVERVIEW OF PROFESSIONAL SOCIETY GUIDELINES

From the primary search strategy, the PubMed query resulted in 531 articles (date of query 2023-08-16). The manual selection process yielded one additional article (American Academy of Pediatrics [AAP] 2020 practice parameter on DD [15]). Of the 532 total articles, nine met inclusion criteria and 523 were excluded. The PRISMA 2020 Flow Diagram is shown in Figure 1. Characteristics of the nine included articles are shown in Table 1 and details of the genetic testing recommendations within each article are outlined in Table 2.

There are certain guidelines we included and excluded that warrant comment. We did include the American Academy of Child and Adolescence Psychiatry (AACAP) 2014 guidelines focused on ASD [16] among these nine articles. According to the AACAP, “by standard convention, Practice Parameters become outdated after five years” (https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx). However, we decided to keep this article as one of the included studies, given that (1) there was not explicit mention of this parameter being retired either in the full text of the article or in its enclosing website (https://www.jaacap.org/article/S0890-8567(13)00819-8/fulltext) (2) practitioners may not be aware of this AACAP-specific policy of retired guidelines after five years and thus may still access the full text/PDF of the guideline for application in clinical practice. We decided to include both the 2014 AAP guideline on GDD/ID [17] and the 2020 AAP guideline on DD [18], as the latter is a more general statement of developmental disorders and covers diagnosis, management as well as etiological evaluation, whereas

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the former is specifically focused on GDD/ID and etiological evaluation. We did not include a 2010 statement on etiological evaluation for DD/ID, ASD, and multiple congenital anomalies [9], as this statement was by an international organization (International Standard Cytogenomic Array Consortium), and we included only U.S. statements.

The publication years ranged from 2000 to 2022, and only five guidelines were published within the last five years (2018 and onward) [15,19–21]. The nine guidelines were from five medical societies representing four specialties (pediatrics, neurology, medical genetics, and psychiatry): American Academy of Child and Adolescence Psychiatry (AACAP), American Academy of Neurology (AAN), American Academy of Pediatrics (AAP), American College of Medical Genetics and Genomics (ACMG), and Child Neurology Society (CNS). Three guidelines focused exclusively on genetic/etiological evaluation [17,19,22], while the remaining focused on diagnosis, management, and etiological evaluation. There were four society guidelines relevant to individuals with GDD/ID, published between 2014 to 2021 [15,17,19,23]. Four society guidelines focused *exclusively* on ASD [16,21,22,24], and one guideline focused on ASD in addition to GDD/ID [15]. With respect to CP, there was one contemporary society guideline, from the American Academy of Pediatrics (AAP) in 2022 [20]. Out of these nine guidelines, only the ACMG guidelines, published in 2021, firmly recommended WGS or ES as a first-tier test for unexplained NDDs [19]. We inferred several themes from these guidelines discussed below.

RESULTS: MANY PROFESSIONAL SOCIETY GUIDELINES ARE OUTDATED

Many society-based practice guidelines discussing genetic testing for NDDs (specifically GDD/ID, ASD, and CP) are more than five years old. One of the four society guidelines pertaining to individuals with GDD/ID, the AAP 2014 guidelines on GDD/ID [17], is from 10 years ago. A 2003 guideline on GDD from the AAN and CNS [25] was retired and thus excluded from our scoping review; no updated guideline on GDD from these societies was identified. Among the five guidelines including ASD, only two were from the past five years: the AAP 2020 guidelines on DD [15] and the AAP 2020 guidelines on ASD [21]. For CP, there was one recent society guideline, from the AAP in 2022 [20]. A 2004 guideline on CP from the AAN [26] was retired and thus excluded from our scoping review; no updated guideline on CP from the AAN was identified. In summary, out of a total of nine practice guidelines published between 2000 and 2022, only 5/9 (55%) were from the past five years.

RESULTS: RECOMMENDATIONS DO NOT REFLECT CONTEMPORARY KNOWLEDGE

The most recently published guidelines for an NDD often do not reflect contemporary knowledge and/or availability of modern genetic testing options. For example, ES became available as a clinical test in 2011, and in 2013, the first clinical WGS became available in the U.S. (Figure 2). More recently, converging data from different disorders (NDDs or otherwise) supports first-line broad testing with ES or WGS especially to aid in narrowing a differential diagnosis or making a molecular diagnosis (the exception is that if there is a specific genetic condition like Down syndrome under consideration based on the phenotype,

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then targeted testing for that condition should occur first). However, numerous guidelines still do not reflect this paradigm shift in genomic evaluation.

With one exception, the most recent society guidelines pertaining to GDD/ID have recommended non-NGS technologies as first-tier genetic tests, including the following:

- CMA and Fragile X testing (AAP 2014 guidelines focused on GDD/ID [17]; AAP 2020 guidelines focused on DD [15]; 2020 AACAP guidelines focused on GDD/ID [23])

The one exception is the ACMG 2021 guidelines, recommending ES/WGS as a first- or second-tier test for patients with DD, ID, or congenital anomalies [19]. The AAP 2020 guidelines focused on DD (including GDD and ASD) [15] do indicate that, for GDD/ID, "further testing [after CMA and Fragile X] may include ES and gene panels" without making a definitive recommendation.

The most recent society guidelines pertaining to ASD have also recommended non-NGS technologies as first-tier genetic tests, including:

- Karyotype, Fragile X testing, or CMA (AACAP 2014 guidelines focused on ASD [16])
- Karyotype and Fragile X testing (AAN and CNS 2000 guidelines focused on ASD [24])
- CMA and Fragile X testing (AAP 2020 guidelines focused on ASD [21]; AAP 2020 guidelines focused on DD including GDD and ASD [15]; ACMG 2013 guidelines focused on ASD [22])

Recent guidelines on CP from the AAP 2022 [20] referenced genetic testing for a subset of patients ("diagnostic evaluation may include advanced genetic techniques, such as chromosomal microarray and genomic sequencing") but did not provide detailed guidance for when this is indicated or the specific type of genetic testing that should be pursued.

RESULTS: RECOMMENDATIONS DIVERGE ACROSS SPECIALITIES

It is notable that for a given NDD, there are differing recommendations for genetic testing depending on which society created them. These variations may arise as a result of the familiarity of providers in that specialty with new testing methodologies, consideration of the severity of the patients typically seen by that specialty, and differences in the year of publication as noted above. For example, a neurologist evaluating a patient with ASD may reference the most recent guidelines by the society pertinent to their specialty (i.e., CNS or AAN) [24], which would suggest karyotype and Fragile X testing as first line testing. A pediatrician seeing the same patient may reference the 2020 AAP guideline on ASD [21] and consider sending CMA and Fragile X testing. If the patient has co-occurring ID (a common scenario given that 30–70% of children with ASD have ID [27]), a geneticist may adhere to the ACMG 2021 guidelines [19] and consider sending ES or WGS. As a result of these divergent recommendations, the same patient may undergo different sets of genetic testing depending

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on the referring clinicians who may be following practice guidelines most closely associated with their specialty.

DISCUSSION: NEGATIVE IMPACT FROM LACK OF CONTEMPORARY GUIDELINES

The lack of contemporary, consistent, unified guidelines from medical societies on genetic testing for NDDs may have detrimental impacts on patients due to missed or delayed diagnosis of genetic conditions. There is high likelihood that this impact is inequitable on the basis of social determinants of health, including insurance coverage, race/ethnicity, rurality, economic and employment status, and educational background. Here, we will discuss the implications of missing and/or delaying a genetic diagnosis; outline ways in which the lack of contemporary, consistent guidelines could contribute to missed/delayed genetic diagnoses; and discuss how these effects could be felt inequitably among various demographic groups, leading to disparities in care.

Why is early identification of a genetic diagnosis as the cause of NDD important?

This question is perhaps best answered through review of the potential benefits of a genetic diagnosis for children with NDDs. First, for all children who receive a genetic diagnosis, there is termination of the “diagnostic odyssey”, which parents find valuable in and of itself [28]. Beyond providing an answer for why a child has an NDD, a genetic diagnosis may lead to changes in medical management, surveillance, reproductive counseling, family testing, access to clinical trials/research, access to therapy services, access to advocacy/support groups, and reduced healthcare costs [6,29–32]. The reported frequency of these outcomes varies greatly due to heterogeneous study definitions, but a meta-analysis found that 27%, 17%, and 6% of patients underwent a change in clinical management following results of WGS, ES, and CMA, respectively [31]. These rates are only expected to increase over time as precision therapies are developed and research accumulates regarding best practices for rare neurogenetic disorders. The timeliness of the genetic diagnosis must also be emphasized, as earlier diagnosis is the first step toward earlier implementation of appropriate management, which is particularly critical in NDDs, where the neuroplasticity of infancy and early childhood can be leveraged to allow for optimal developmental achievement.

How does the lack of *contemporary* guidelines contribute to missed/delayed genetic diagnoses?

Namely, guidelines that do not recommend first-line use of the most effective current technology for genetic diagnosis in NDD are likely to lead to missed or delayed genetic diagnoses in clinical care. The diagnostic yields of different testing methods for NDDs have been established through systematic reviews and meta-analyses, with ES/WGS yielding several-fold higher diagnostic rates than CMA for individuals with non-specific presentations [4–6]. With regard to multi-gene panels, as the number of identified NDD-related genes continues to expand with improving technology and pooling of patient samples [33,34], ES and especially WGS are becoming increasingly more useful in comparison. Furthermore, while it may seem intuitive that ES/WGS would report more variants of unknown significance (VUS) compared to multi-gene panels, the opposite has been reported,

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likely reflective of higher rates of concurrent parental sample availability and higher phenotypic correlation required for generating ES/WGS reports [35]. Beyond ES/WGS, there are emerging newer technologies, such as long-read WGS, transcriptomics, polygenic risk scores, and epigenetic profiling, which are under investigation in terms their clinical utility [36–39]. There is also increasing identification of genetic "dual diagnoses" among NDD patients, in which patients are found to have more than one genetic condition [40]. This must be considered among patients with phenotypes atypical for their genetic diagnosis, and additional testing or reanalysis of initial testing should be pursued. The genetic landscape of NDDs is rapidly changing, and future guideline development/revision should mirror this pace, since both clinicians' genetic testing practice decisions[41] and insurance coverage policies [13,14,42] are influenced by professional guidelines. If guidelines do not recommend first-line use of the most effective and efficient genetic testing technology, less effective/efficient testing types will be used instead, leading to missed or delayed diagnoses.

How does the lack of *consistent* guidelines contribute to missed/delayed genetic diagnoses?

Inconsistencies between society guidelines allow payers to implement coverage policies that still "align with society guidelines" but are not reflective of best practice. Clinicians often recognize best practices but run into limitations in implementation due to insurance difficulties. For example, in a 2021 survey of 172 U.S child neurologists, 65% supported ES as a first-line diagnostic test for NDDs, but only about 10% reported routinely obtaining it, with many citing insurance coverage as a major barrier[43]. Furthermore, in a sample of 4,500 prior authorizations for genetic testing in Texas, one-third of ES requests were denied due to lack of medical necessity, characterization of such testing as experimental/investigational, or not meeting criteria for testing per the payer rules [44]. Interestingly, in the Texas study, the inclusion of specific diagnostic codes when submitting a prior authorization request did not influence the outcome of the prior authorization decision, *except* in the instance of the International Classification of Diseases, Tenth Revision (ICD-10) code for Autism (F84.0) in requests for CMA testing, which was associated with a higher approval rate [44]. This potentially reflected payers' incorporation of outdated society guidelines recommending CMA as a first-line test for ASD within their coverage plans. Moreover, with a broad swathe of guidelines for genetic testing for NDDs that have differing recommendations, insurance companies are incentivized to cherry-pick support for recommendations within certain guidelines that may be less costly, but not necessarily more beneficial. Cost-effectiveness studies for different types of genetic testing – while not the focus of this review – may help address this concern. For example, a recent study demonstrated that WGS as a first-line test for children with suspected genetic disorders is cost-effective compared to other testing strategies (including first-line ES)[45]. If a unified, regularly updated cross-society guideline existed, and individual societies routinely retired outdated guidelines, insurance providers would have fewer reputable sources to back coverage policies that lead to missed and delayed genetic diagnoses.

How does the lack of contemporary, consistent guidelines contribute to health disparities?

Racial/ethnic disparities have been well-documented among children with NDDs, affecting diagnosis rates/settings (healthcare vs. school), age at diagnosis, access to therapy services,

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and access to subspecialists [46–51]. Socioeconomic factors, such as insurance status/type, income, parent education, and geographic region, have also been shown to be associated with therapy and subspecialty service usage [48,52,53]. Research specifically evaluating disparities in access to genetic testing for NDDs has been limited to date, but there is some evidence of inequities, with children identified as Black/African American or Hispanic less likely to receive genetic testing compared to non-Hispanic White children [54–57]. There are extensive barriers to genetic testing, many of which disproportionately affect individuals with historically marginalized identities, who face added challenges related to systemic racism [58]. Complex diagnostic pathways requiring additional subspecialty referrals have been shown to relate to racial disparities in genetic testing [59,60]. Society guidelines failing to promote the highest yield test as the first-tier test may lead to additional visits as part of the diagnostic odyssey, potentially widening existing health disparities for individuals with NDDs [61,62]. Though diagnostic yield is not the only metric for choice of a first-line genetic test (for example, other metrics include cost, cost/diagnostic yield, and availability/accessibility of the test), it is nonetheless a predominant consideration. Furthermore, lack of consistency among guidelines likely contributes to the known substantial variability in specialty providers' use of genetic testing for NDDs [43,63,64], since professional guidelines are reported as highly influential in physicians' genetic testing practice [41]. Practice variability may drive inequities in care, as patients receive different evaluations based on access to specialists rather than differences in their clinical presentations (with the hypothesis that one particular medical specialist might reference a guideline published by a society affiliated with their specialty). Based on this analysis and recommended previously[65], we suggest that societies combine efforts to create a joint guideline, with representation from multiple specialties, with processes in place to allow regular updates via online reports.

RECOMMENDATIONS

Based on the above results, examples from adjacent clinical fields, and the authors' collective expertise in the care of children with NDDs, we have created a series of recommendations for medical societies engaged in the development or updating of genetic testing practice guidelines.

1. Professional societies could combine efforts to create a single guideline.

We propose the formation of a national committee on genetic testing for NDDs, composed of experts nominated by members of relevant professional medical societies across specialties including neurology, psychiatry, developmental behavioral pediatrics, primary care pediatrics, rehabilitation medicine, and genetics. This approach, along with efforts to increase provider education, would likely provide more uniformity between practitioners caring for individuals with NDD. We suggest creation of a publicly-available committee website that will serve as the publication site for unified guidelines, allowing frequent updates and reducing redundancy intrinsic to the current guideline development processes of different societies. There is tremendous work that goes into the creation or updating of a society guideline, including administration, guidance from methodologists, literature search, data analysis, writing, editing, legal review, and attribution of credit. Thus, this

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idea would help reduce duplication of effort. One example of such a combined approach is from 2015, when the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) worked together to establish guidelines for reporting sequence variants [66]. Another example is the creation of guidelines for using descriptions of race, ethnicity, and ancestry in genetics research, based on involvement of editors from multiple different biomedical journals [67]. A unified, single guideline could be disseminated through the creation of an online resource, such as what has been done for the Children's Oncology Group (https://childrensoncologygroup.org/cog-supportive-care-endorsed-guidelines), with information about this resource disseminated by each of the medical societies involved to its members.

2. Medical societies could formally endorse other societies' genetic testing practice guidelines.

Endorsement of an existing guideline may minimize duplication of effort while promoting cross- or intra-disciplinary collaboration. For example, with respect to epilepsy, the National Society of Genetic Counselors (NSGC) published a practice guideline in 2023 recommending ES/WGS and/or a multi-gene panel (>25 genes) as a first-tier test, followed by CMA if the initial testing was non-diagnostic [68]. The American Epilepsy Society has also endorsed this guideline. This endorsement increases the guideline's impact by promoting awareness among members of both societies. Endorsement of existing guidelines for genetic testing for an NDD does not preclude the creation or updating of separate guidelines that focus on other aspects of the NDD, like diagnosis and management.

3. Medical societies could consider creating/updating practice guidelines for genetic testing separately from guidelines that are disorder-specific and focused on other aspects of diagnosis or management.

For example, the ACMG 2021 guidelines recommend ES/WGS as a first- or second-tier test for all individuals with DD/ID and/or congenital anomalies [19]. These guidelines outline the evidence behind this genetic testing recommendation but do not discuss other aspects of care, such as screening, imaging, other lab work, medications, or surveillance for associated conditions. In contrast, the most recent AAP guidelines on developmental surveillance and screening embed a discussion of genetic testing for children with DD [15]. A separate statement on genetic testing specifically would allow for easier, more frequent updates and provide a quicker reference point to clinicians.

4. Medical societies should strongly consider the genetic heterogeneity and phenotypic overlap of NDDs in the development of genetic testing guidelines.

The number of genes associated with NDDs continues to rapidly expand, as do the phenotypes of individual genetic disorders (e.g., *MECP2*-related disorders in individuals without Rett syndrome[69], GLUT1 deficiency in individuals with mild learning difficulties and other milder phenotypes [70], among other examples). Due to this, we suggest broad spectrum evaluation with ES/WGS as first-line testing for individuals with unexplained NDDs and non-specific features.

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5. Medical societies could structure their guidelines to inform payer coverage policies that are aligned with clinical best practices.

Given that payer medical policies often cite clinical guidelines [71], medical societies should be aware of how their guidelines influence access to testing. Guidelines should clearly delineate the clinical benefits of genetic testing and the ability of such testing to guide clinician decision-making and recommendations for follow-up care, as well as the value of genetic testing to patients and families. Given the quick pace of progress in genetic technologies, payers would benefit from additional clinical input, particularly regarding the diagnostic sensitivity of various assays for genomic anomalies of interest [72]. We recommend medical societies notify payers when both systematic evidence reviews and evidence-based practice guidelines are published in an effort to promote timely development of evidence-based payer policies and reduce coverage-based disparities in access to genetic testing. It may be helpful for medical societies to reach out to payers prior to writing a guideline to learn more about how payers review and incorporate guidelines when writing medical policies. A general understanding of payer perspectives on medical societies guidelines can be helpful in the structuring of a guideline that is aligned with clinical best practices. While it is not within the scope of medical societies to tell payers what to cover, medical societies do have a responsibility to make sure payers have the most up-to-date guidelines available when writing medical policy. As technology and the understanding of the genetic contributions to human health and disease continue to advance at a rapid pace, it can be challenging for clinicians and payers to keep up with the advancements if medical societies do not educate and inform them through new practice guidelines. This is critical to preventing patients and families from delays in receiving the newest standards of care. The National Society of Genetic Counselors recently began sending letters to state Medicaid directors to inform them of new Expanded Carrier Screening Guidelines to be considered when reviewing Medicaid policies on this type of genetic testing [73]. Raising awareness of new guidelines to other medical societies and payers is helpful for endorsements as well as consideration of new medical policies.

6. Genetic testing practice guidelines could specifically address recommendations for improving access among marginalized patient populations.

Further research is required to investigate reasons for disparities in access to and uptake of genetic testing among marginalized population groups and the relationship between access to genetic testing and structural determinants of health. However, societies could acknowledge potential barriers that disproportionately affect marginalized groups, and as more research accumulates, suggest targets for intervention to increase equitable access. One way of increasing access to genetic services may be with the addition of telehealth options. Telehealth, especially in remote areas or locales without nearby tertiary medical centers, may increase use of genetic counseling, based on one study examining utilization of genetic services via telehealth vs. usual care options at oncology clinics without direct access to genetic counseling [74].

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7. Medical societies with guidelines pertaining to genetic testing should strive to update or reaffirm guidelines every 3–5 years.

This cadence, while frequent, is reflective of the rapid evolution of genetic/genomic technologies. There is precedent in this update cadence: according to the Evidence-Based Clinical Practice Guideline Development Manual for the National Society of Genetic Counselors (NSGC), "The [Practice Guideline Committee] reviews NSGC's practice guidelines every five years and will initiate the review process three-to-four years after the original guideline's publication date, and every three-to-four years thereafter, to allow ample time for revision, if necessary" (https://www.nsgc.org/Portals/0/Docs/NSGC%20PG%20Manual%20Revision%20-%20March%202020.pdf). If a society is unable to reaffirm or update a specific guideline, it can endorse more updated guidelines from another society in the interim. The importance of frequent updates to genetics-related practice guidelines is underscored by the rapid pace of genomic discoveries and technologies over the past two decades. Dozens of genes are discovered each year to be associated with disorders in the context of pathogenic variants [75]. On a daily basis, approximately 10 new genetic tests are made available in the U.S. and global markets [76,77].

8. An online resource should be created to track ongoing recommendations for genetic testing for NDDs.

This could be modeled off the National Comprehensive Cancer Network (NCCN)'s extensive online guideline process, which includes guidelines related to genetic testing and involves continual review and updates to ensure they are reflective of current evidence [78]. This approach would ensure that NDD society guidelines include the most updated evidence and are quickly accessible to clinicians and payers. Ideally, these guidelines would be reflected in coverage plans across all insurance providers, which could minimize the contribution of insurance status to inequities in access to genetic testing.

LIMITATIONS

Our work has a few notable limitations. First, we focused exclusively on U.S.-based genetic testing guidelines due to the differences between healthcare systems and payment structures in other countries. Nonetheless, the principles outlined in this review, including the need for modernized guidelines across specialties for different NDDs, may still be relevant to healthcare systems in different countries. Second, we limited our scoping review to include only GDD/ID, ASD, and CP, three major NDDs for which there is scientific evidence regarding the utility of genetic testing. Over time, our scientific knowledge may expand to include an understanding of the yield of genetic testing for other NDDs, such as ADHD[79], reiterating the need to continually update and revise society guidelines. We did not evaluate primary data used to develop these guidelines. Third, we acknowledge that improvements in professional society guidelines for genetic testing for NDDs must be accompanied by provider education and advocacy among policymakers in order to have optimal impact on clinical care. Providers often cite lack of genetic knowledge/confidence as a reason for lack of testing or referring for genetic testing [63,64,80]. For non-geneticists, education efforts should include both "standard" and intensive training options, depending on providers' intentions to order/interpret/disclose testing on their own or alongside a

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genetic counselor, or refer to genetic counseling for testing only. For non-geneticists, guidelines for the interpretation and communication of genetic testing results should be established and included in provider education programs. Beyond educational deficiencies, providers also cite insurance barriers as a major reason for lack of genetic testing usage [41,43,80]. Engagement with payer administrators to highlight evidence of cost effectiveness [81] alongside diagnostic and management benefits may be helpful [82]. Within oncology genetic testing and payer coverage, there has been a call for incorporating regularly-updated society guidelines in the health technology assessment process used in coverage decision-making [83]. A similar approach should be considered for NDDs. Fourth, we acknowledge that the spectrum and diagnostic yield of genetic testing for other NDDs, such as attention deficit hyperactivity disorder (ADHD) and specific learning disabilities, are not addressed in this scoping review but should be added in the future as additional literature regarding these disorders is published. Fifth, we acknowledge that societal guideline updates may be in progress that are not reflected in this article. For example, the American Academy of Neurology and Child Neurology Society are working on updated quality measures for genetic testing for GDD/ID, epilepsy, and CP.

CONCLUSION

Genetic testing remains a rapidly evolving field with falling costs and improved diagnostic yields. Like other clinical guidelines, an appropriate balance must be struck between the current evidence base and flexibility to remain relevant over time. As the applications of genetic testing have greater impact on early diagnosis and intervention, there must be a greater involvement of all stakeholders, including payers, policymakers, and family advocacy groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Data from this scoping review is available upon request from the corresponding author.

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Summary for Social Media If Published

1. If you and/or a co-author has a Twitter handle that you would like to be tagged, please enter it here. (format: @AUTHORSHANDLE).
   a. Jordan Cole: @JordanJanaeCole
2. What is the current knowledge on the topic? (one to two sentences)
   a. Neurodevelopmental disabilities (NDDs) are one of the most common conditions affecting children seen by pediatric neurologists. Genetic testing for NDDs is critical for diagnosis, medical management, and access to precision therapies. Professional society guidelines serve an essential role in guiding clinical genetic testing; however, several challenges exist regarding guideline creation and maintenance.
3. What question did this study address? (one to two sentences)
   a. No synthesis of current US professional society guidelines pertaining to genetic testing for neurodevelopmental disabilities exists. We aimed to fill this gap and provide an assessment of the contemporaneity and consistency of current US guidelines across societies.
4. What does this study add to our knowledge? (one to two sentences)
   a. Of nine current US professional society guidelines pertaining to genetic testing for neurodevelopmental disabilities, only five (55%) were published within the last five years, and most recommend first-line testing that is not consistent with contemporary evidence regarding the superiority of exome/genome sequencing for patients with non-specific presentations.
5. How might this potentially impact on the practice of neurology? (one to two sentences)
   a. We propose strategies and recommendations for the improvement of professional society guideline processes to optimize their timeliness, utility, and accessibility. Adoption of these strategies could lead to improved insurance coverage and improved ability for clinicians to keep up with the rapidly-evolving landscape of genetic testing.

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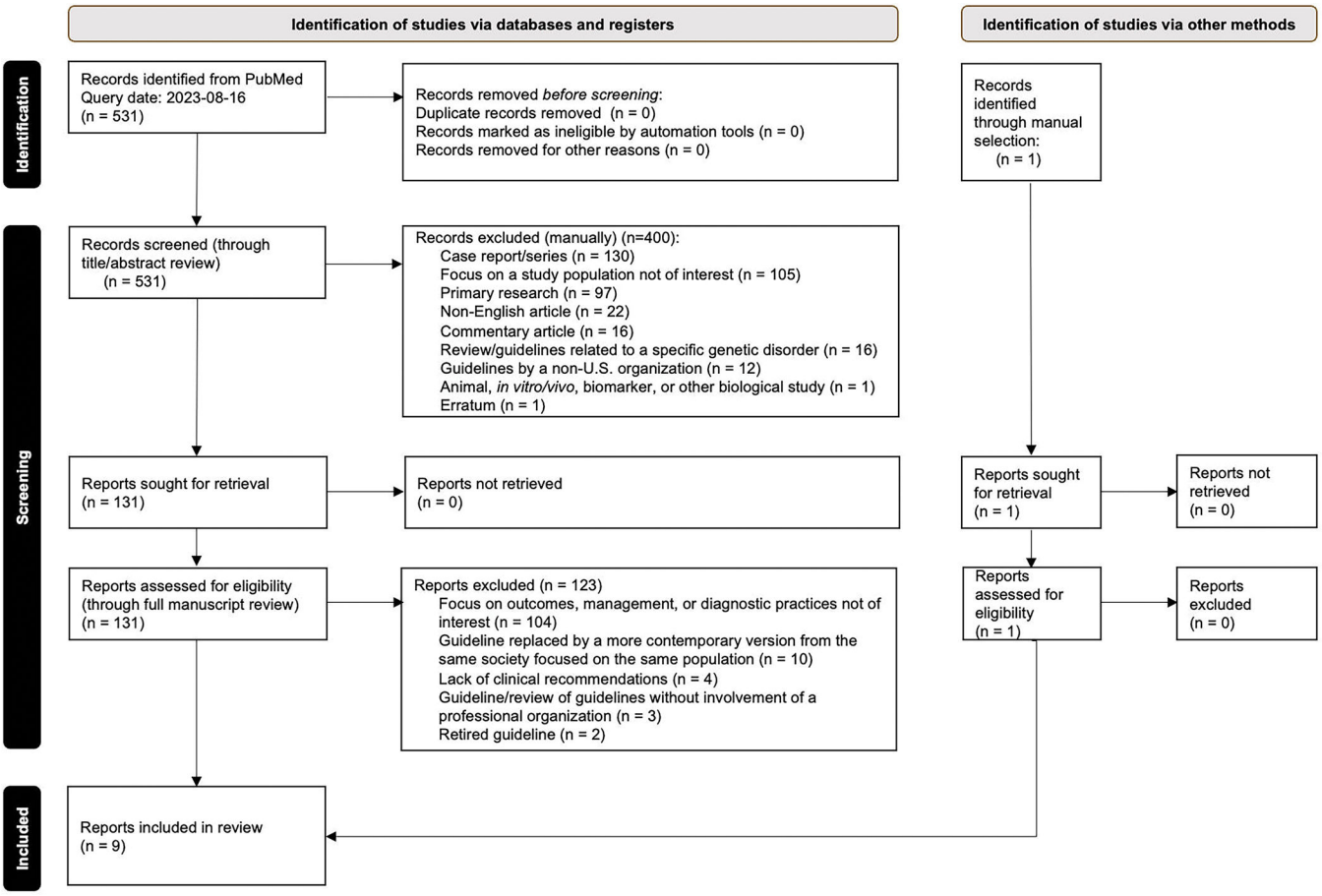

Figure 1.
PRISMA diagram showing identification of studies used in the scoping review.

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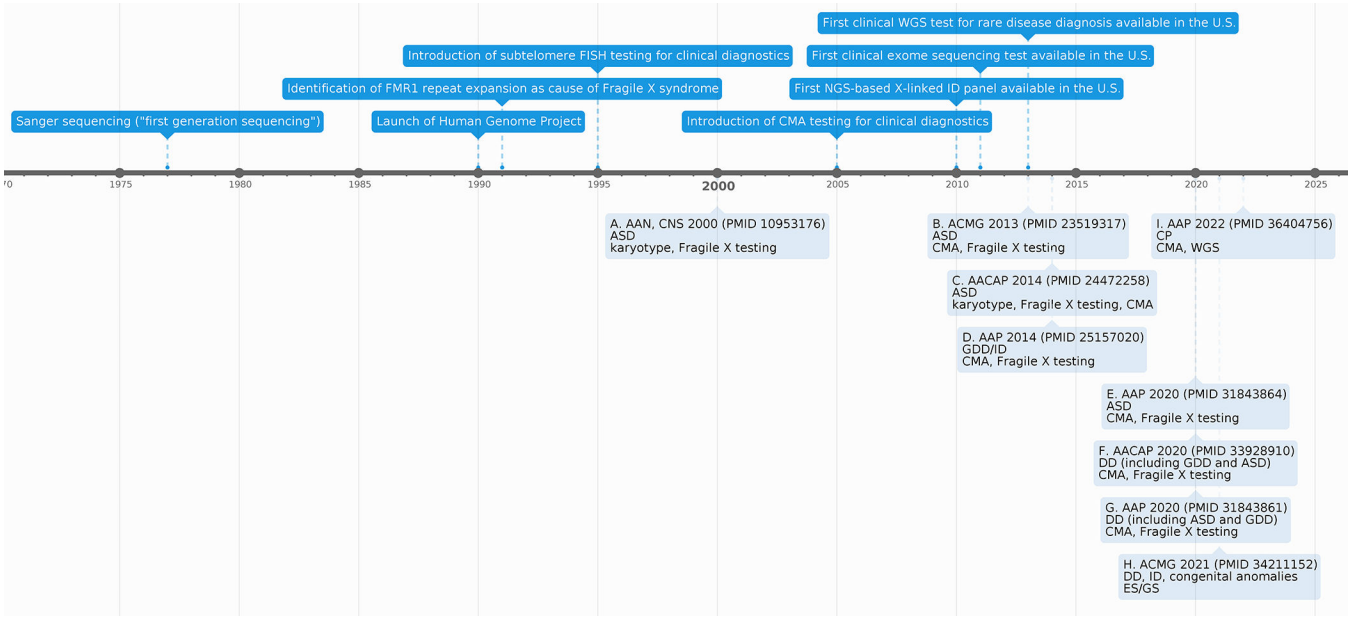

Figure 2.

Timeline depicting the advent of different genetic sequencing technologies (top) and year of publication of different NDD practice parameters (bottom). The letter in front of each guideline cross-references the respective entries in Table 1.

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Table 1.

Characteristics of nine professional society guidelines with information on genetic testing for neurodevelopmental disorders.

	Year	Society	Title	Target Population	Focus of Recommendations	1st Line Test(s) Discussed
A **10953176**	2000	American Academy of Neurology (AAN) & Child Neurology Society (CNS)	Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society	ASD	Diagnosis, management, etiological evaluation	Karyotype, Fragile X testing
B **23519317**	2013	American College of Medical Genetics and Genomics (ACMG)	Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions	ASD	Etiological evaluation	CMA, Fragile X testing (males only)
C **24472258**	2014	American Academy of Child and Adolescent Psychiatry (AACAP)	Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder	ASD	Diagnosis, management, etiological evaluation	Karyotype, Fragile X testing, CMA
D **25157020**	2014	American Academy of Pediatrics (AAP)	Comprehensive evaluation of the child with intellectual disability or global developmental delays	GDD/ID	Etiological evaluation	CMA, Fragile X testing
E **31843864**	2020	American Academy of Pediatrics (AAP)	Identification, Evaluation, and Management of Children With Autism Spectrum Disorder	ASD	Diagnosis, management, etiological evaluation	CMA, Fragile X testing
F 33928910	2020	American Academy of Child and Adolescent Psychiatry (AACAP)	Practice Parameter for the Assessment and Treatment of Psychiatric Disorders in Children and Adolescents With Intellectual Disability (Intellectual Developmental Disorder)	GDD/ID	Diagnosis, management, etiological evaluation	CMA, Fragile X testing (referencing other guidelines)
G **31843861**	2020	American Academy of Pediatrics (AAP)	Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening	DD (including but not limited to GDD and ASD)	Diagnosis, management, etiological evaluation	CMA, Fragile X testing
H **34211152**	2021	American College of Medical Genetics and Genomics (ACMG)	Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)	DD, ID, Congenital anomalies	Etiological evaluation	ES/WGS
I **36404756**	2022	American Academy of Pediatrics (AAP)	Providing a Primary Care Medical Home for Children and Youth With Cerebral Palsy	CP	Diagnosis, management, etiological evaluation	CMA, WGS (not firmly recommended)

Pubmed ID is included in column on the far left. ASD = autism spectrum disorder; CP = cerebral palsy; DD = developmental delay; GDD = global developmental delay; ID = intellectual disability; CMA = chromosomal microarray; ES = exome sequencing; WGS = whole genome sequencing.

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Table 2.

Details of genetic testing recommendations within nine professional society guidelines related to neurodevelopmental disorders.

	Year	Society	Target Population	Detailed Recommendations
A 10953176	2000	American Academy of Neurology (AAN) & Child Neurology Society (CNS)	ASD	1. Send karyotype and fragile X testing if there is co-occurring ID (or if ID cannot be excluded), family history of fragile X syndrome or undiagnosed ID, or dysmorphic features. 2. Send metabolic testing in specific circumstances.
B 23519317	2013	American College of Medical Genetics and Genomics (ACMG)	ASD	1. Perform a three-generation family history with pedigree analysis. Perform comprehensive history and physical evaluation. If a specific syndrome is suspected, send targeted testing. Perform metabolic and/or mitochondrial testing if suggestive clinical indicators. 2. If autism is unexplained, send CMA as a first-tier test for all patients and fragile X testing for males. 3. Second tier testing as follows: *MECP2* sequencing for all females. *MECP2* duplication testing in males if phenotype is suggestive. *PTEN* testing if head circumference is > 2.5 SD above mean.
C 24472258	2014	American Academy of Child and Adolescent Psychiatry (AACAP)	ASD	1. Perform medical assessment, including physical examination, a hearing screen, a Wood's lamp examination, and genetic testing, which may include karyotype, fragile X testing, or CMA.
D 25157020	2014	American Academy of Pediatrics (AAP)	GDD/ID	1. Perform comprehensive history and physical examination. If specific diagnosis is certain, inform the family. If specific diagnosis is suspected, send targeted testing. 2. If no specific diagnosis is suspected, CMA and fragile X testing should be first-line tests in all. Consider metabolic testing (round 1). 3. If family history is suggestive of X-linked disorder, send X-linked ID panel and high-density X-CMA. Consider testing for X-inactivation skewing in the mother of the proband. If the patient is female, send *MECP2* sequencing and deletion/duplication analysis.
E 31843864	2020	American Academy of Pediatrics (AAP)	ASD	1. Consider immediate referral to clinical genetics to guide genetic evaluation. 2. If pursuing first-tier testing oneself, perform comprehensive history and physical examination. If specific diagnosis is suspected, send targeted testing. 3. If no specific diagnosis is suspected, discuss and offer CMA and fragile X analysis. If family history is suggestive of X-linked disorder, refer to clinical genetics. If patient is female, consider *MECP2* testing. 4. If first-tier tests are unrevealing, consider referral to genetics, workup might include ES.
F 33928910	2020	American Academy of Child and Adolescent Psychiatry	DD (including GDD and ASD)	1. Perform complete neuropsychiatric evaluation. 2. If no specific diagnosis is suspected, send CMA and fragile X testing. 3. If testing is non-diagnostic, consider additional testing, such as ES, karyotype, or mitochondrial DNA testing.
G 31843861	2020	American Academy of Pediatrics (AAP)	DD (including GDD and ASD)	1. For suspected GDD/ID or ASD, perform CMA and fragile X testing as first-tier tests. 2. For suspected GDD/ID, consider metabolic testing if indicated by history and physical examination. 3. For suspected GDD/ID, second-tier testing may include ES and gene panels. For suspected ASD, consider genetics consultation.
H 34211152	2021	American College of Medical Genetics and Genomics (ACMG)	DD, ID, Congenital anomalies	1. ES/WGS should be a first- or second-tier test in all patients with unexplained DD/ID or congenital anomalies.
I 36404756	2022	American Academy of Pediatrics (AAP)	CP	1. Diagnostic evaluation may include CMA or genome sequencing.

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