# Clinical Diagnostic Genetic Testing for Individuals With Developmental Disorders

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Nearly 1 in 5 individuals with developmental disorders (DDs; including autism spectrum disorders, intellectual disability [ID], and global developmental delay [GDD]) are estimated to have an identifiable and clinically relevant genetic risk factor.[1,2] Diagnostic genetic testing, which seeks to establish a molecular diagnosis, is standard-of-care for all individuals with unexplained (idiopathic) DD, as recommended by multiple professional organizations, including the American Academy of Child and Adolescent Psychiatry (AACAP),[3] the American Academy of Pediatrics,[4] and the American College of Medical Genetics (ACMG).[1] A molecular diagnosis can provide direct benefit to the patient, because some genetic syndromes require targeted treatments (e.g., phenylketonuria), whereas others have practice parameters available to manage medical and behavioral symptoms (e.g., Rett syndrome). Indirect benefits of a molecular diagnosis include better estimates of the recurrence risk for DD in family members and opportunities to join diagnosis-specific trials and support organizations.

## RELEVANCE TO CHILD PSYCHIATRIC PRACTICE

Child psychiatrists are trained to integrate the psychiatric, behavioral, and medical care of people with DD. For many child psychiatrists, there remains a critical knowledge gap in understanding the rationale for molecular genetic testing and whether further testing is indicated. To aid child psychiatrists in their clinical practice, the AACAP Autism and Intellectual Disability Committee has summarized the guidelines for diagnostic genetic testing in people with DD. For guidance on other aspects of the evaluation of DD, see AACAP Practice Parameters for autism spectrum disorder[3] and ID (in preparation). The recommendations summarized here apply only to diagnostic genetic testing and not to pharmacogenomic testing, which predicts a patient's response to medications from gene panel testing and has minimal evidence base for use in DD.

## ASSESS NEED FOR FURTHER DIAGNOSTIC GENETIC TESTING

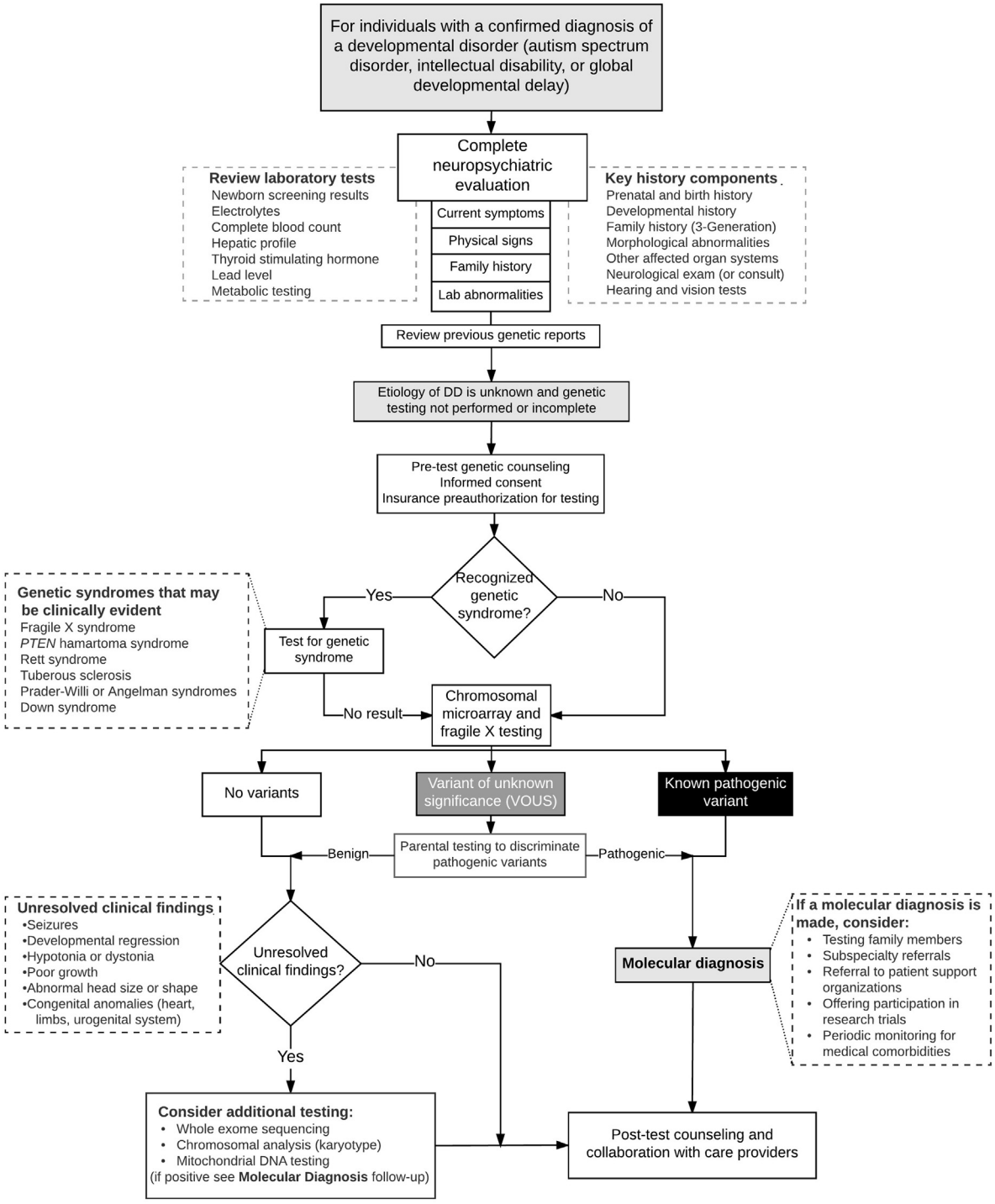
Child psychiatrists routinely synthesize the medical, developmental, and psychological histories of their patients to formulate a clinical impression and treatment plan. For those patients with DD of undetermined etiology, standard-of-care guidelines recommend diagnostic genetic testing to determine a molecular diagnosis. The medical history (including any previously performed genetic tests) and physical examination (performed by the psychiatrist or documented by the patient's medical providers) can guide the need for further genetic testing. If a complete genetics evaluation was not previously performed, then our consensus workflow (Figure 1) presents a generic algorithm for diagnostic genetic testing.[1,3-5] Care collaboration with the patient's primary care provider and/or referral to a medical geneticist will aid in implementing these guidelines for individual patients.

## RECOMMENDATIONS FOR TIERED DIAGNOSTIC GENETIC TESTING

Before completing diagnostic genetic testing, informed consent must be obtained by a trained genetic counselor from the patient and/or family, including potential benefits (see above) and risks of testing. The risks of testing include the likelihood of no actionable findings, spurious results that prompt unnecessary testing, discovery of non-paternity if family members are tested to determine carrier status, and the possibility of identifying incidental risk factors for diseases unrelated to DD (e.g., breast cancer risk or Huntington disease).

1. The recommendation for Tier 1 standard of care genetic testing in individuals with a confirmed clinical diagnosis of autism spectrum disorder, ID, and/or GDD of unknown etiology includes:
   - Chromosomal microarray in all individuals (regardless of sex, IQ, or co-occurring medical conditions) to identify microdeletions and micro-duplications in the genome (copy number variants)
   - Fragile X gene testing in all boys and in girls with ID or a family history of ID
2. Certain factors noted during history or physical examination might suggest a specific genetic diagnosis and require different tests, such as:
   - *PTEN* (phosphatase and tensin homolog) gene testing if head circumference is more than 2.5 standard deviations above the mean for age
   - *MECP2* (methyl CpG binding protein 2) gene testing for Rett syndrome in girls with severe ID
   - Karyotype analysis if a chromosomal syndrome is suspected

**FIGURE 1** Diagnostic genetic testing algorithm for youth with developmental disorders (DDs). *Note*: Recommendations for genetic testing in people with autism spectrum disorder, global developmental delay, and intellectual disability according to the American College of Medical Genetics,[1] the American Academy of Child and Adolescent Psychiatry,[3] the American Academy of Neurology,[5] and the American Academy of Pediatrics.[4] *PTEN* = phosphatase and tensin homolog.



3. Alternatively, if Tier 1 genetic studies return with no clinically relevant findings and the patient has evidence of unresolved medical findings (Figure 1), then further testing can be performed:
   - Sequencing of all genes in the genome (whole exome sequencing)
   - Determining whether rare imprinting or mitochondrial syndromes are present

Whole exome sequencing is likely to become an additional Tier 1 standard-of-care test as costs decrease, because it can detect small changes in DNA sequence that chromosomal microarray cannot detect. When assessed in the aggregate, more than 1 in 5 individuals with DD can be expected to have a positive finding from at least 1 of the genetic tests listed above. However, clinicians should remain aware that these tests do not assess for all heritable genetic traits that are associated with DD (e.g., a genetic change outside the regions detected with whole exome sequencing but too small to be detected by chromosomal microarray).

## INTERPRETATION OF RESULTS AND POST-TEST FOLLOW-UP

The clinical report of the results will include a listing of pathogenic genetic changes (or variants) and any incidental findings in genes classified as clinically actionable by the ACMG.[6] Clinical information gathered by the medical team is crucial to determine whether identified variants are pathogenic. Clinical geneticists consider the type and functional effect of the genetic variant, whether similar variants have previously been reported in people with DD or other relevant conditions, and whether the change is present in other affected family members to determine whether the variant is pathogenic or benign. Some identified variants are clearly pathogenic (such as disruptive *PTEN* or *MECP2* mutations), whereas other variants have not previously been associated with DD and are termed "variants of unknown significance." If a variant of unknown significance is present in an unaffected biological parent, then the genetic change is less likely to contribute to the etiology of the DD, and further testing can be considered. Post-test genetic counseling is recommended for all cases in which results (benign, variants of unknown significance, or pathogenic) are returned.

If a test is positive for a specific molecular diagnosis, then the collaborative care team can consult published guidelines for specific syndromes (e.g., fragile X syndrome), refer to appropriate medical providers, refer family members for genetic testing and counseling, recommend patients to clinical trials and support networks, and/or encourage families to submit their test results to national registries to increase awareness of known pathogenic variants.

## CONCLUSIONS

Familiarity with diagnostic genetic testing is a new but essential skill for child psychiatrists. Although medical geneticists remain the best equipped to perform a comprehensive diagnostic genetic evaluation, psychiatrists play an increasing role in the regular care of individuals who stand to benefit from a molecular genetic diagnosis. Therefore, we have concisely summarized key aspects of current genetic testing recommendations in this population in an easily accessible format for clinicians. Going forward, we anticipate that diagnostic genetic testing will be an increasingly essential component of the evaluation and management of patients with DD. &

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