This is a summary of the American Academy of Neurology and Child Neurology Society evidence report regarding genetic and metabolic testing in children with global developmental delay (GDD) and/or intellectual disability (ID).

Please refer to the full evidence report at www.aan.com for more information.

**Genome-wide Genetic Testing**

<table>
<thead>
<tr>
<th>Microarray studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microarray testing is abnormal on average in 7.8% of subjects with GDD/ID (27 Class III studies†).</td>
</tr>
<tr>
<td>Microarray testing is abnormal in 10.6% of those with syndromic features (18 Class III studies).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G-banded karyotype studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype studies are abnormal in at least 4% of subjects with GDD/ID (1 Class II study).</td>
</tr>
<tr>
<td>Karyotype studies are abnormal in 18.6% of those with syndromic features (9 Class III studies).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subtelomeric fluorescence in situ hybridization studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtelomeric fluorescence in situ hybridization (StFISH) testing is abnormal in 5.9% of unexplained GDD/ID (1 Class I study).</td>
</tr>
<tr>
<td>StFISH testing is abnormal in at least 7.4% of those with moderate/severe impairment (1 Class I study).</td>
</tr>
<tr>
<td>StFISH testing is abnormal in as few as 0.5% of those with mild impairment (1 Class I study).</td>
</tr>
<tr>
<td>StFISH testing is abnormal in at least 3.5% of subjects with either GDD/ID or multiple congenital anomalies (37 Class III studies).</td>
</tr>
<tr>
<td>In subjects with syndromic features, StFISH had a yield of 4.2% (1 Class II study) and 5.4% (1.3%–20%) (11 Class III studies).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X-linked ID gene studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR1 testing has a combined yield of at least 2% in male and female subjects with mild GDD/ID (4 Class II and 17 Class III studies).</td>
</tr>
<tr>
<td>MeCP2 mutations are found in 1.5% of girls with moderate/severe GDD/ID (4 Class III studies) and in less than 0.5% of males with GDD/ID (9 Class III studies).</td>
</tr>
<tr>
<td>Mutations in X-linked genes may explain up to 10% of all cases of GDD/ID. Testing of X-linked ID (XLID) genes has a yield of 42% in males from definitely X-linked families and of 17% in males from possibly X-linked families (1 Class III study).</td>
</tr>
</tbody>
</table>

**Metabolic Testing**

<table>
<thead>
<tr>
<th>Inborn errors of metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for inborn errors of metabolism (IEMs) in children with GDD/ID has a yield of between 0.2% and 4.6%, depending on the presence of clinical indicators and the range of testing performed (7 Class III studies).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Congenital disorders of glycosylation and disorders of creatine metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing for congenital disorders of glycosylation has a yield of up to 1.4%, and testing for creatine synthesis and transport disorders has a yield of up to 2.8% (2 Class III studies).</td>
</tr>
</tbody>
</table>
Clinical Context

We reviewed numerous studies that found yields of more than 1% for various genetic and metabolic tests in children with unexplained GDD/ID. Most of the studies were classified as providing Class III evidence because their subjects were drawn from referral-based neurology and genetics specialty clinics, where most decisions regarding testing are and will continue to be made. The yield of a given test is admittedly only one of many factors to be considered when planning a diagnostic testing strategy for a child with GDD or ID. Other factors include the ability of a test to identify a treatable disorder; the pretest probability of presence of a disease based on clinical features and family history; and the availability, invasiveness, and cost of testing.

The figure below provides a clinical guide to diagnostic test selection.

Figure. Algorithmic evaluation of unexplained global developmental delay or intellectual disability

Unexplained global developmental delay/intellectual disability

A) Obtain detailed medical and developmental history, including prior diagnostic testing, especially newborn screening labs
B) Elicit three-generation family history
C) Conduct complete physical and neurologic examination with attention to dysmorphism
D) Consider EEG testing if history is concerning for epileptic seizures or encephalopathy
E) Consider psychoeducational testing, vision testing, and hearing testing
F) Consider referral to a clinician with relevant expertise if child appears to have an unrecognized genetic syndrome

Specific etiology suspected?

Yes

A) Genetic syndrome: single-gene tests
B) XLID: XLID gene testing
C) Structural abnormality: MRI
D) Metabolic disorder: screening tests

Abnormal

Test parents and siblings as appropriate
Refer for genetic counseling

No

Diagnostic

Perform specific testing as appropriate

Neuroimaging: Head MRI; if available, consider MRS

Normal

Perform metabolic testing on the basis of clinical judgment:
A) Plasma amino acids, ammonia, and acylcarnitines
B) Serum uric acid
C) Urine organic acids
D) Urine and plasma creatine, creatinine, and guanidinoacetic acid
E) Appropriate testing for CGDs
F) Plasma VLCFA, piperocil acid, phytanic acid, and RBC plasmalogens
G) Serum 7-dehydrocholesterol
H) Urine mucopolysaccharides and sialic acid
I) Blood or fibroblast screening for lysosomal enzyme deficiencies
J) CSF glucose, lactate, pyruvate, glycine, organic acids, folate, and neurotransmitter metabolites

Abnormal

Perform specific testing as appropriate

Normal

Conduct ongoing follow-up
Consider further evaluation as warranted
Consider referral to a medical geneticist

XLID = X-linked intellectual disability;
StFISH = subtelomeric fluorescence in situ hybridization;
MRS = magnetic resonance spectroscopy;
CGDs = chronic granulomatous disorders;
VLCFA = very long chain fatty acid;
RBC = red blood cell
An etiologic diagnosis for GDD or ID only occasionally leads to a specific therapy that improves the child’s outcome; however, it often leads to other benefits for the child and the child’s family. These benefits include relieving caregivers of anxiety and uncertainty, empowering caregivers to become involved in support and research networks, limiting further diagnostic testing that may be costly or invasive, improving understanding of treatment and prognosis, anticipating and managing associated medical and behavioral comorbidities, allowing for counseling regarding recurrence risk, and preventing recurrence through screening for carriers and prenatal testing.

The evaluation of children with neurodevelopmental disabilities is evolving as previously unrecognized disease mechanisms are uncovered and novel and increasingly sensitive methods for diagnosis are introduced, improving etiologic yields. Physicians who develop their familiarity with the clinical features and testing of genetic and metabolic disorders will likely be more efficient in their patient evaluations, ordering fewer tests rather than more. Many children seen for GDD/ID do not present with syndromic features or a positive family history.

Microarray is the genetic test with the highest diagnostic yield in children with unexplained GDD/ID. The resolution of the current generation of commercially available, genome-wide, oligonucleotide-based microarray testing is 700 base pairs, 30 to 40 times higher than the oligo-based tests previously used in studies of GDD/ID and 1000 times higher than older bacterial artificial chromosome–based microarrays. Laboratories now offer single nucleotide polymorphism sensitive microarray that detects and describes consanguinity or uniparental disomy. Studies on the yield of these more advanced microarray tests are anticipated in the near future. Currently, microarray testing can identify only unbalanced copy number changes and is insufficiently sensitive for detecting genetic disorders caused by inversions, balanced insertions, reciprocal translocations, polyploidy, low-level mosaicism (<20%–25%), rearrangements in repeat sequences, point mutations, or duplications/deletions that are undetectable at the test’s resolution level. The results of microarray testing are often complex and require confirmation and careful interpretation, often with the assistance of a medical geneticist.

The other genome-wide genetic tests reviewed, G-banded karyotyping and StFISH testing, have a lower sensitivity for abnormalities in similar populations of children with unexplained GDD/ID. There is consensus among clinical geneticists that microarrays should be considered first-line cytogenetic tests, preferred over StFISH testing and karyotyping, with karyotyping reserved for patients having signs of a specific chromosomal syndrome (e.g., Down syndrome), a family history of a chromosomal rearrangement, or a parent with a history of multiple miscarriages.

Males with a history strongly suggestive of X-linked inheritance may be considered for testing of one or more individual XLID genes or for screening of the entire X chromosome. Girls with severe impairment may be appropriate for testing for MeCP2 mutations, regardless of whether the specific clinical features of Rett syndrome are present.

There may be greater suspicion for IEMs in children whose parents either are consanguineous or have had children with similar problems or unexplained death or fetal demise. Children with IEMs may have multiple organ system dysfunction, failure to thrive, dietary selectivity, unusual odors, hearing loss, or episodic symptoms, including seizures or encephalopathy. The importance of considering IEMs requires emphasis, because for some entities specific dietary or metabolic treatments may improve neurologic symptoms.

In addition to the clinical matters considered above it is important to remember that genetic testing is costly and may not be available to all families. Some of the critical matters related to the cost analysis of performing microarray testing are summarized in appendix e-11 of the published evidence report.

†Classification of Evidence for Screening Studies

Class I: A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients’ clinical presentations.

Class II: A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients’ clinical presentations.

Class III: A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

This is an educational service of the American Academy of Neurology (AAN). It is designed to provide members with evidence-based guidance to assist with decision-making in patient care. It is based on an assessment of current scientific and clinical information and is not intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physicians caring for the patient, based on the circumstances involved. Physicians are encouraged to review carefully the full AAN evidence reports and guidelines so they understand all recommendations associated with care of their patients.