Autism, Intellectual Disability, and Developmental Delay Genetic Testing

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Introduction

Autism, intellectual disability, and developmental delay genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures covered by this guideline	Procedure codes
AFF2 gene analysis; evaluation to detect abnormal (eg, expanded) alleles	81171
AFF2 gene analysis; characterization of alleles (eg, expanded size and methylation status)	81172
Autism Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Autism Known Familial Mutation Analysis	81403

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Procedures covered by this guideline	Procedure codes
Developmental Delay Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Developmental Delay Known Familial Mutation Analysis	81403
Intellectual Disability Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Intellectual Disability Known Familial Mutation Analysis	81403
X-linked Intellectual Disability Duplication/ Deletion Analysis Panel	81471
X-linked Intellectual Disability Sequence Analysis Panel	81470

Criteria

Introduction

Requests for Autism Spectrum Disorder (ASD), Intellectual Disability (ID), and Developmental Delay testing are reviewed using the following clinical criteria.

Known Familial Mutation Testing

- Genetic counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for the known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Known family mutation in a causative gene in 1st, 2nd, or 3rd degree biological relative, OR
- Prenatal Testing for At-Risk Pregnancies:
  - Known familial disease-causing mutation identified in both biological parents (if recessive), or a single biological parent or an affected sibling of the pregnancy (if dominant), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Autism, Intellectual Disability and Developmental Delay Single Gene Diagnostic Tests (Sequencing and Deletion/Duplication)

- The member has a formal diagnosis of ASD/autism, intellectual disability, and/or developmental delay as made by an appropriate health care professional, AND
- The member has a condition that will benefit from information provided by the requested gene testing based on the following:
  - The member displays at least one clinical feature (in addition to autism, intellectual disability, and/or developmental delay) of the suspected condition for which testing is being requested, AND
    - The member's medical management would be significantly altered by the genetic diagnosis, or
    - A particular treatment is being considered for the member that requires a genetic diagnosis, OR

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- The member meets all criteria in a test-specific guideline, if available (see the Table below for a list of genes, associated conditions, and applicable guidelines), AND

- The member does not have a known underlying cause for their symptoms (e.g. known genetic condition), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Autism, Intellectual Disability, and Developmental Delay Multi-Gene Panels

X-Linked Intellectual Disability Panels

Targeted panels consisting solely of genes associated with X-linked intellectual disability (XLID) are medically necessary when all of the following criteria are met:

- Individual assigned male at birth, AND
- The member has a formal diagnosis of ASD/autism, intellectual disability, and/or developmental delay as made by an appropriate health care professional, AND
- The member has a family history of ASD/autism, intellectual disability, and/or developmental delay of unknown etiology consistent with X-linked inheritance, AND
  - The member's medical management would be significantly altered by the genetic diagnosis, or
  - A particular treatment is being considered for the member that requires a genetic diagnosis, AND
- The member does not have a known underlying cause for their symptoms (e.g. known genetic condition), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Comprehensive Autism, Intellectual Disability, and/or Developmental Delay Panels

Multi-gene panels for individuals with a primary medical diagnosis of ASD, ID, and/or GDD (global developmental delay) have not demonstrated a high diagnostic yield and are not likely to lead to a change in treatment. Comprehensive ASD and/or ID/GDD panels, regardless of panel size, are experimental, investigational, or unproven (E/I/U).

Separate clinical guidelines may apply to other panel testing and exome sequencing for members who have findings in addition to ASD/ID/GDD, such as seizures or multiple congenital anomalies (see Other Considerations and Table: *Common neurodevelopmental disorder genes, associated conditions, and applicable guidelines*).

Other Considerations

- ASD, ID, and/or GDD testing may be performed as part of a chromosomal microarray, exome sequence, or genome sequence. For information on these tests, please refer to the guidelines *Chromosomal Microarray Testing For Developmental Disorders (Prenatal and Postnatal)*, *Exome Sequencing*, or *Genome Sequencing*, as these tests are not addressed here.
- Genetic testing is only medically necessary once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- This guideline may not apply to genetic testing for indications that are addressed in test-specific guidelines. Please see the test-specific list of guidelines for a complete list of test-specific panel guidelines.

Table: Common neurodevelopmental disorder genes, associated conditions, and applicable guidelines

This list is not all-inclusive.

Gene	CPT	Condition	Applicable guideline name	Applicable guideline number
15q11.2	81331	Prader-Willi Syndrome, Angelman Syndrome	Prader-Willi Syndrome testing; Angelman Syndrome Testing10059	MOL.TS.217; MOL.TS.126
AFF2	81171 81172	Fragile X Syndrome 2 (FRAXE)	Autism, Intellectual Disability, and Developmental Delay Genetic Testing	MOL.TS.269
BRAF	81406	Noonan Syndrome, Cardiofaciocutaneous Syndrome	Noonan Spectrum Disorder Genetic Testing	MOL.TS.371
CHD7	81407	CHARGE Syndrome	CHARGE Syndrome and CHD7 Disorder Genetic Testing	MOL.TS.324

Gene	CPT	Condition	Applicable guideline name	Applicable guideline number
FMR1	81243 81244	Fragile X Syndrome	FMR1-Related Disorders (Fragile X) Genetic Testing	MOL.TS.172
MECP2	81302	Classic Rett Syndrome, Preserved Speech Variant Rett Syndrome, MECP2-Related Epileptic Encephalopathy (males), X-Linked ID	Rett Syndrome Genetic Testing 10629	MOL.TS.224
NF1	81408	Neurofibromatosis 1	Neurofibromatosis Type 1 Genetic Testing	MOL.TS.301
PTEN	81321	PTEN Hamartoma Tumor Syndromes	PTEN Hamartoma Tumor Syndrome Genetic Testing 10192	MOL.TS.223
PTPN11	81406	Noonan Syndrome	Noonan Spectrum Disorder Genetic Testing	MOL.TS.371
UBE3A	81406	Angelman Syndrome	Angelman Syndrome Genetic Testing 10059	MOL.TS.126

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a

claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Comprehensive Autism Spectrum Disorder panels, Intellectual Disability/Developmental Delay panels, and Neurodevelopmental Disorder panels, regardless of how they are billed, are not reimbursable.
- When otherwise reimbursable, the following limitations apply:
    - Any individual gene or multi-gene panel is only reimbursable once per lifetime.
    - When an X-linked intellectual disability panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81470/81741*).
    - When use of a panel code is not possible, each billed component procedure will be assessed independently.
    - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

Note *The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are Autism Spectrum Disorders, Intellectual Disability, and Global Developmental Delay?

Definition

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in communication and social interaction, as well as restricted, repetitive patterns of behavior, interests, or activities. Intellectual disability (ID, formerly referred to as mental retardation) is "a disability characterized by significant limitations in both intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills."[1] Global developmental delay (GDD) categorizes younger children (typically less than 5 years of age) who have significant delay (characterized as performance two standard deviations or more below the mean on age-appropriate, standardized, normal-referenced testing) in two or more developmental domains, including gross or fine motor, speech and language, cognitive, social and personal, and activities of daily living.[2]

Incidence

ASD affects approximately 1/54 children.[3] ID affects 1-3% of the population worldwide.[2] The incidence of GDD is estimated to be comparable to ID.[1,4] All three neurodevelopmental disorders are more common in males.[2,4-7]

Symptoms

ASD was previously divided into categories that included autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder- not otherwise specified (PDD-NOS). With current diagnostic criteria, these categories were subsumed under the diagnosis of ASD.

Symptom onset is in early childhood (typically before 3 years of age).[6,7] ASD is often accompanied by intellectual disability, behavioral difficulties, and/or sensory abnormalities.

ID and GDD may present in infancy or early childhood. ID is assessed in three domains: intelligence (IQ), adaptive behavior, and systems of supports the individual requires.[1] Children with GDD have significant delay in two or more developmental domains. Young children with GDD may later be diagnosed with ID and/or ASD.[2,4] There are both syndromic and non-syndromic forms of inherited ASD, ID, and GDD. The constellation of associated findings is highly dependent on the underlying etiology. Clinical information (e.g. presence of specific congenital malformations, dysmorphic features, and other symptoms) may be used in some cases to help narrow down the suspected cause. In these cases, it may be possible to identify a narrow subset of genes that may be responsible for an individual's neurodevelopmental concerns.

Cause

ASD, ID, and GDD can develop secondary to head injury, birth complication, endocrine disorder (e.g., hypothyroidism), toxic exposure (e.g., fetal alcohol syndrome), inborn error of metabolism (e.g., phenylketonuria), and central nervous system infection.[2,6,7]

There are also many known genetic conditions that are associated with an increased risk for ASD, ID, and GDD. A thorough clinical genetics evaluation is estimated to result in an identified cause in 30–40% of affected individuals with ASD.[6] Chromosome microarray analysis was previously thought to have the highest diagnostic yield of any single test for these disorders, with an estimated detection rate of at least 10-20% for ASD, ID, and GDD (often grouped together as neurodevelopmental disorders, or NDDs).[4,6,8,9] Whole exome and genome sequencing have more recently been demonstrated to have diagnostic yields of up to 35% for those with NDDs and potentially higher for those with other comorbidities such as epilepsy or congenital anomalies.[9]

Inheritance

Inheritance patterns differ between the various syndromes associated with ASD, ID, GDD. Inherited forms of these disorders can show autosomal dominant, autosomal recessive, X-linked, or mitochondrial patterns of inheritance.

Diagnosis

ASD, ID, and GDD are diagnosed through the evaluation of an individual's development and behaviors by an appropriate specialist (such as neurodevelopmental pediatrician or developmental-behavioral pediatrician). Medical tests such as hearing screening, vision screening, and neurological evaluations may also be performed.[2,5] A diagnosis of ASD and/or ID is often difficult to establish in infants and very young children, as the standardized methods used for diagnosis are less reliable in children under the age of 5 years; the term "global developmental delay" is thus used to categorize these individuals.[2] Identifying an underlying genetic etiology for an individual's NDD cannot provide a diagnosis of ASD versus ID versus a specific learning disability.

Management

Management for ASD includes behavioral interventions such as applied behavioral analysis (ABA) therapy, structured educational interventions, and in some cases, pharmacotherapy.[6,7] NDDs are also managed with therapies and educational intervention plans tailored to the individual's needs. In a limited number of cases (mostly metabolic disorders), knowing the genetic mutation that is responsible for a neurodevelopmental disorder can help to guide management. Identifying a genetic syndrome may also alert the healthcare team to potential comorbidities for which evaluation and surveillance may be needed.

Survival

While life expectancy in autism may be reported as reduced, this is often secondary to accidents such as drowning.[3] With the exception of individuals with multiple disabilities (such as Down syndrome), the life expectancy of individuals with intellectual disability is now similar to that of the general population.[10] Comorbid conditions can also affect survival in these disorders.

Test information

Introduction

Testing for ASD, ID, and GDD may include known familial mutation analysis, single gene sequence analysis, single gene deletion/duplication analysis, or multi-gene panels of various sizes.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

ASD, ID and GDD multi-gene panels include a wide variety of genes: from a few to hundreds or even thousands. These disorders may also be grouped together in broad "neurodevelopmental" panels. Multi-gene panels may also include genes believed to be associated with disease (e.g. "susceptibility" genes), but with a lower impact on risk than recognized syndromes. Results for such genes are of less clear value because there often are not clear management recommendations for mutation-positive individuals.

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to testing for ASD, ID, and GDD.

American Academy of Child and Adolescent Psychiatry

The American Academy of Child and Adolescent Psychiatry (AACAP, 2014) stated that as a clinical standard, clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD to include:[5]

- "All children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray."
- "Unusual features in the child (e.g., history of regression, dysmorphology, staring spells, family history) should prompt additional evaluations… Genetic or neurologic consultation, neuroimaging, EEG, and additional laboratory tests should be obtained when relevant, based on examination or history (e.g., testing for the MECP2 gene in cases of possible Rett's disorder)."

American Academy of Child and Adolescent Psychiatry

The American Academy of Child and Adolescent Psychiatry (AACAP, 2020) recommended a diagnostic genetic testing algorithm for youth with developmental disorders (autism spectrum disorder, intellectual disability, or global developmental delay):[11]

- If there is a recognized genetic syndrome, targeted testing is recommended first. This could include a karyotype if Down syndrome is suspected.
- In the absence of a recognized syndrome, or if testing is unrevealing, then chromosomal microarray and Fragile X testing are recommended as the next step.
- "Microarray is currently the genetic test with the highest diagnostic yield in children with unexplained ID/IDD, with an abnormal result reported in 7.8% of subjects with GDD/ID/IDD and in 10.6% of those with syndromic features, on average."

American Academy of Pediatrics

The American Academy of Pediatrics (AAP, 2014, Reaffirmed 2019) recommended a clinical genetics evaluation for all individuals with ID, regardless of degree of severity.[4]

- "If a specific diagnosis is suspected, arrange for the appropriate diagnostic studies to confirm including single-gene tests or chromosomal microarray test."

- "If diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process:
    - Chromosomal microarray should be performed in all.
    - Specific metabolic testing should be considered and should include serum total homocysteine, acyl-carnitine profile, amino acids; and urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, GAA/creatine metabolites.
    - Fragile X genetic testing should be performed in all."
- "If no diagnosis is established:
    - Male gender and family history suggestive X-linkage, complete XLID panel that contains genes causal of nonsyndromic XLID and complete high-density X-CMA. Consider X-inactivation skewing in the mother of the proband.
    - Female gender: complete MECP2 deletion, duplication, and sequencing study."

The American Academy of Pediatrics (AAP, 2020) recommended the following for the evaluation of children with ASD:[7]

- "Families should be offered genetic evaluation, including chromosomal microarray and fragile X testing, with consideration of other cytogenetic and molecular testing, as indicated. Consultation with a pediatric geneticist may be warranted."

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2013) recommended a genetic evaluation, with a tiered approach, for all individuals with diagnosed ASD:[6]

- "Several well-described single-gene disorders have been reported for which ASDs can be seen as part of the expanded phenotype associated with changes in that gene...For a selected few of such conditions, there is adequate evidence to suggest testing for changes in these genes in patients with ASDs with no other identifiable etiology. These would include fragile X syndrome, methyl-CPG-binding protein 2 (MECP2) spectrum disorders, and phosphatase and tensin homolog (PTEN)–related conditions."
- First tier:
    - Three-generation family history with pedigree analysis.
    - Initial evaluation to identify known syndromes or associated conditions:
        - Examination with special attention to dysmorphic features
        - If specific syndromic diagnosis is suspected, proceed with targeted testing

        - If appropriate clinical indicators present, perform metabolic and/ or mitochondrial testing (alternatively, consider a referral to a metabolic specialist)
    - Chromosomal microarray: oligonucleotide array-comparative genomic hybridization or single-nucleotide polymorphism array.
    - DNA testing for fragile X (to be performed routinely for males and in females if indicators are present - e.g., family history and phenotype).
- Second tier:
    - MECP2 sequencing to be performed for all females with ASDs
    - MECP2 duplication testing in males, if phenotype is suggestive
    - PTEN testing only if the head circumference is >2.5 SD above the mean
    - Brain magnetic resonance imaging only in the presence of specific indicators (e.g., microcephaly, regression, seizures, and history of stupor/coma)
- “When a family history is consistent with X-linked inheritance and the patient has cognitive impairments, an “X-linked intellectual disability gene panel” is a consideration. Several X-linked genes are known to present as either ASD or intellectual disability. Another disorder to consider is the X-linked creatine transporter defect (SCL6A8 gene). Patients with this condition have been reported with neurobehavioral changes in the ASD spectrum, along with hypotonia and seizures. Currently, no studies have been reported on the diagnostic yield of such panels in persons with ASDs."
- The following are genetic tests “that have been suggested in the etiologic evaluation of ASDs, but currently with insufficient evidence to recommend routine testing:” CDKL5 testing, NSD1 testing, chromosome 15 methylation/UBE3A gene testing, methylation/epigenetic testing, mitochondrial gene sequencing/oligoarray, and metabolic studies.

The American College of Medical Genetics and Genomics (ACMG, 2021) developed an evidence-based clinical practice guideline for the use of exome and genome sequencing (ES/GS) in the care of children with one or more congenital anomalies (CA) with onset prior to age one year, or development delay (DD) or ID with onset prior to 18 years.[12]

- ES/GS is strongly recommended as a first- or second-tier test for children with CA/ DD/ID.
- "Consistent with existing guidelines/recommendations/position statements, patients with clinical presentations highly suggestive of a specific genetic diagnosis should undergo targeted testing first. This may include patients with suspicion of a chromosomal disorder, known family history of a disorder, or strong clinical suspicion of a diagnosis in which sequencing may not be diagnostic, such as Prader–Willi/Angelman related methylation abnormality or fragile X syndrome."

- "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation."

The National Institute for Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE, 2017) stated the following regarding medical investigations following diagnosis of an ASD: “Do not routinely perform any medical investigations as part of an autism diagnostic assessment, but consider the following in individual circumstances and based on physical examination, clinical judgment, and the child or young person's profile:[13]

- Genetic tests, as recommended by your regional genetics center, if there are specific dysmorphic features, congenital anomalies and/or evidence of intellectual disability.
- Electroencephalography if there is suspicion of epilepsy."

Selected Relevant Publications

A 2017 peer reviewed article assessed the clinical utility of a targeted gene panel (101-237 genes) in 100 well-phenotyped individuals with ASD, and found:[14]

- 12% diagnostic yield for chromosomal microarray
- 0% diagnostic yield for targeted gene panel (11 pathogenic variants identified; all assessed as non-causative by clinicians based on clinical evaluation of the individuals, allele frequency in the study population, or conflicting data in the literature on causation)
- If the individual does not fit a syndromic diagnosis, the authors suggested ACMG recommended tests followed by whole exome sequencing in individuals with ASD plus
    - Severe disability
    - Congenital abnormalities
    - Comorbid conditions (eg: seizure disorder)
    - Abnormal head size

A 2019 meta-analysis published the diagnostic yield of exome sequencing compared to chromosomal microarray for neurodevelopmental disorder (NDD, defined as GDD, ID, and/or ASD) and found: [8]

- The yield of exome sequencing overall was 36%, markedly greater than previous studies of chromosomal microarray (15-20%).
- The diagnostic yield in individuals with isolated NDD was 31% and 53% for individuals with NDD plus associated conditions (such as Rett-like features).

A 2021 systematic review published results of clinical sequencing studies utilizing targeted gene panel sequencing and exome sequencing in individuals with epilepsy, ASD, or ID.[15] Of the 103 studies included, 73 utilized targeted gene panels and 36 used exome sequencing.

- The overall diagnostic yield was 23.7% (17.1% for ASD, 24% for epilepsy, and 28.2% for ID).
- Although not statistically significant, the diagnostic yield for exome sequencing was higher than for panel sequencing (27.2% vs 22.6%, P = .071).

A 2022 peer-reviewed article assessed different genetic testing strategies for individuals with ID and/or NDD.[9] Three cohorts of individuals underwent testing. The three strategies included chromosomal microarray with or without FMR1 analysis (421 individuals), genome sequencing as a secondary testing (129 individuals), and genome sequencing first (100 individuals).

- The diagnostic yield was 11% for individuals who underwent chromosomal microarray / FMR1 analysis, 26% for individuals who underwent genome sequencing as a secondary test, and 35% for individuals who underwent genome sequencing as a first test.

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Introduction

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