Clinical Policy Title: Genetic testing for autism spectrum disorders

Clinical Policy Number: 11.04.02

Effective Date: January 1, 2014
Initial Review Date: July 16, 2014
Most Recent Review Date: August 19, 2015
Next Review Date: August 19, 2016

Related policies:
Policy 02.01.03 Array Comparative Genomic Hybridization Testing.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

- Select Health of South Carolina considers the use of genetic testing for autism spectrum disorders to be clinically proven and, therefore, medically necessary when all of the following criteria are met:
  - There is clinical evidence of autism spectrum disorder meeting the criteria of the Diagnostic and Statistical Manual - Fifth Edition (DSM-V) (see Background).
  - There is a care-coordinating, multidisciplinary team trained in autism available for genetic and behavioral counseling for a tiered evaluation, which includes (a.) a primary care physician, (b.) a geneticist (who is a physician or a licensed genetic counselor), (c.) behavioral health specialists, (d.) speech/language testing and (e.) developmental/neurologic assessment.
  - Family desire for engagement with the integrated multidisciplinary team as documented in the clinical record.
- Select Health of South Carolina considers neuroimaging for screening of patients with autism spectrum disorder in the absence of confounding neurologic presentation or dysmorphic
features to be not clinically proven and, therefore, not medically necessary. The use of MRI and other neuroimaging studies for diagnosis of specific conditions may be considered on an individual basis. (Examples: neuroimaging may be approved for a patient with ASD who also has a seizure disorder, or a patient with tuberous sclerosis.)

- Select Health of South Carolina considers the use of low-yield, syndrome-specific genetic testing for prenatal screening to be not clinically proven and, therefore, not medically necessary.
- When ordered by a non-geneticist, Select Health of South Carolina considers the use of the syndrome-specific genetic tests below to be not clinically proven in the diagnosis of autism spectrum disorders:
  - CDLK5 testing.
  - Cholesterol/7 dehydrocholesterol.
  - Chromosome 15 methylation/UBE3A gene testing.
  - Methylation/epigenetic testing.
  - Mitochondrial gene sequencing/oligoarray.
  - NSD1 testing.
  - Reduction-oxidation studies.
  - Screening for disorders of purine/pyrimidine metabolism (serum and urine uric acid).
  - Screening for folate-sensitive fragile sites.
  - Selected neurometabolic screening (mucopolysaccharides, creatinine phosphokinase, amino acids, organic acids, lactate, ammonia, acylcarnitine profile).

Limitations:

All other uses of genetic testing for autism spectrum disorders are not medically necessary.

Alternative covered services:

In-network visits to primary care physicians, behavioral health specialists, genetic counselors, as well as routine laboratory testing.

Background

Autism spectrum disorder (ASD) is a highly prevalent condition, estimated by the Centers for Disease Control (CDC) at one in 68 children, and is three to four times more common in boys. ASD represents the phenotypic expression of a variety of pervasive neurologic developmental disorders and is not a singular diagnosis. Typically, the manifestations of ASD become obvious in early childhood, but may not become evident until later in childhood, adolescence or even adulthood. The condition appears to have both genetic and environmental etiologies. Under 2013 revisions to the DSM-V the criteria for consideration of autism spectrum disorder involve both communication disorders and a high degree of sensitivity to routine and repetitive behaviors (see new DSM-V criteria above).
### Checklist

#### DSM-V criteria for the diagnosis of autism spectrum disorders

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<tr>
<td><strong>A.</strong> Deficits in use or understanding of social communication and social interaction in multiple contexts, not accounted for by general developmental delays, and manifest by all three of the following:</td>
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<tr>
<td>1.</td>
<td>Deficits in nonverbal communicative behaviors used for social interaction, ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body language or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.</td>
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<td>2.</td>
<td>Deficits in social-emotional reciprocity, ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions and affect and response to total lack of initiation of social interaction.</td>
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<td>3.</td>
<td>Deficits in developing and maintaining relationships appropriate to developmental level (beyond those with caregivers), ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people.</td>
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<td><strong>B.</strong> Restricted, repetitive patterns of behavior, interests or activities as manifested by two of the following:</td>
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<td>1.</td>
<td>Stereotyped or repetitive speech, motor movements or use of objects (examples: simple motor stereotypies, echolalia, repetitive use of objects or idiosyncratic phrases).</td>
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<td>2.</td>
<td>Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change (examples: motoric rituals, insistence on same route or food, repetitive questioning, or extreme distress at small changes).</td>
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<td>3.</td>
<td>Highly restricted, fixated interests abnormal in intensity or focus (examples: strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).</td>
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<td>4.</td>
<td>Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment (examples: apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).</td>
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Centers for Disease Control and Prevention and Oregon Center for Children and Youth with Special Health Needs.

### Epidemiology:
Studies of the epidemiology have suggested multiple possible factors involved with etiology of ASD. There appears to be a bias in the United States of greater percentages of people with ASD whose racial background is African-American, Asian or Hispanic (Becerra) or those who have exposures to pesticides (Shelton). Others have looked at associations of post-traumatic stress disorders in mothers and ASD in their offspring (Roberts). There appears to be a much higher prevalence of recognized ASD in the United States than previously. This may reflect greater sensitivity to the diagnostic criteria or to other inciting factors that are not absolutely clear. The CDC notes the higher prevalence in rather dramatic terms:

![Identified Prevalence of Autism Spectrum Disorder](source)

**Natural history of ASD:**

Autism spectrum disorder is considered to be a lifetime condition impacting the affected individual’s capacity to communicate, interact socially and manage repetitive behaviors. Because it has a range of phenotypic expression, individuals may have significant impairment or be considered “high functioning” with the ability to function in modern society. The latter group is more likely to have a diagnosis made at an older age. ASD is unimproved with pharmacotherapy. However, people with ASD are more likely to have seizure disorders, as ASD is among the more common neurobehavioral comorbidities of children with active epilepsy. Children with ASD are more subject to sleep disorders and gastrointestinal symptoms. All of these may require pharmacotherapy, but the autism spectrum disorder does not. However, core symptoms derived from other comorbid conditions may require other strategies.

There is no “cure” for ASD but the use of a multidisciplinary team can assist the family with understanding and providing the individual with support. Some individuals with ASD learn better coping skills and are able to improve their innate capacity for integration into society.
Etiology of autism spectrum disorders:

ASD is now recognized to have a genetic basis for many individuals, but environmental and social factors play significantly into the expression of autism spectrum disorder. This dual set of causality contributes to the varied expression of the condition. The role of measles-mumps-rubella vaccines has been definitively disproven. Fragile X syndrome is the association of ASD, intellectual impairment and large pinnae of the ears. This is a clear cause for ASD, but only accounts for 1 percent of cases of ASD. There are multiple other genetic causes of autism spectrum disorder. Studies of identical twins have demonstrated the variability of expression, even when the gene pool is the same.

Role of genetic testing:

The American College of Medical Genetics (ACMG) has developed practice guidelines for the identification of the etiology of autism spectrum disorder. The rationale for genetic testing offered by ACMG is that if there is a clear genetic etiology, then the family and patient may focus on developing strategies to improve the life of the affected individual and reduce the potential medical harm of continued testing with its attendant risk of false positives/negatives. ACMG recommends a tiered approach to diagnosis that begins with obtaining a full three-generation family history and pedigree analysis. This is to identify known syndromes or associated conditions (see table below). If such are suggested by this detailed family pedigree, then ACMG recommends performing chromosomal microarray testing. Such a strategy has improved genetic diagnosis from 6 percent to 10 percent in the recent past, to nearly 30 percent or more according to ACMG. However, there are no published studies demonstrating clinical improvements in outcomes of children subjected to such testing, but there are individual cases whereby early initiation of behavioral health interventions, speech therapy and educational assistance do improve the lives of individuals with autism. However, in the presence of comorbid syndromic presentation, genetic testing may be indicated to identify a specific genetic cause and identify other comorbid conditions which may benefit from treatment.

<table>
<thead>
<tr>
<th>Selected genetic syndromes that are known etiologies of autism spectrum disorders</th>
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<tr>
<td>• 22q11.2 deletions including velocardiofacial (Shprintzen) syndrome.</td>
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<td>• Angelman syndrome.</td>
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<td>• CHARGE syndrome.</td>
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<td>• de Lange syndrome.</td>
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<tr>
<td>• Fragile X syndrome.</td>
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<tr>
<td>• MED12 disorders (including Lujan-Fryns syndrome).</td>
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<td>• Prader-Willi syndrome.</td>
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<td>• PTEN-associated disorders (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome).</td>
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<tr>
<td>• Rett syndrome.</td>
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<td>• Smith-Lemli-Opitz syndrome.</td>
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</table>
• Smith-Magenis syndrome.
• Sotos syndrome.
• Tuberous sclerosis.
• PTEN, phosphatase and tensin.


Social and behavioral health strategies:

Studies have demonstrated clinical improvement for individuals who, with their families, successfully engage in a multidisciplinary approach that includes speech and language therapy, behavioral health professionals, and structured educational opportunities through school systems. The major medical societies, as well as the CDC, recommend children with ASD be included in patient-centered medical home models to structure the multidisciplinary team meeting the specific needs of the individual. Many states provide coverage and share information so these teams may not only be aware of the input for team members from different disciplines, but be able to communicate with educational and community resources. In some states, this is not possible because of benefit designs. For example, there is some evidence that music therapy is helpful for children with ASD; however, that is rarely covered by any third party. The outcomes for individuals with autism spectrum disorders may be improved through accurate diagnosis and creation of a network of appropriate medical, educational, linguistic and other individuals.

Searches

Select Health of South Carolina searched PubMed and the databases of:
• UK National Health Services Centre for Reviews and Dissemination.
• Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
• The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on June 25, 2014, using the terms “Autism,” and “Autism Spectrum Disorder.” We included:
• Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
• Guidelines based on systematic reviews.
• Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings
A comprehensive technical review (Sun 2015) examined the impact of genetic testing in unselected mental retardation (MR) referrals, and found that a causative genomic gain or loss is detected in 14—18% of cases. Usually, such chromosomal imbalances arise de novo, are not found in healthy subjects, and have a major impact on the phenotype by altering the dosage of multiple genes. The expected diagnostic yield for patients with autism is about 5% to 10% in nonsyndromic and 10% to 20% in syndromic patients. Exome sequencing in patients with MR or autism revealed de novo mutations in protein coding genes in 60% and 20% of cases, respectively.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| **Sun (2015)** | **Key points:**  
• Technology assessment reviewed evidence for microarray-based comparative genomic hybridization (aCGH), testing for X-linked ID genes, FMR1 testing, MeCP2 testing, and conventional G-banded karyotyping for developmental delays, intellectual disability (ID), or ASD.  
• In patients with global developmental delay (GDD) or ID, microarray testing is diagnostic on average in 7.8%, G-banded karyotyping is abnormal in at least 4%, and subtelomeric fluorescence in situ hybridization is positive in 3.5%.  
• Testing for X-linked ID genes has a yield of up to 42% in males with an appropriate family history. FMR1 testing shows full expansion in at least 2% of patients with mild to moderate GDD/ID, and MeCP2 testing is diagnostic in 1.5% of females with moderate to severe GDD/ID. |
| **Schaefer (2013)** | **Key points:**  
“Accurate diagnosis: It is critical that an accurate diagnosis of ASD be made before initiating the genetic evaluation.”  
• All patients with ASDs should have a formal audiogram to rule out a significant hearing loss.  
• Role of the patient-centered medical home.  
• Referral for clinical genetics evaluation.  
• Tiered evaluation.  
• Genetic counseling.  
• Treatment and follow up. |
| **Myers (2007, 2010)** | **Key points:**  
• “The primary goals of treatment are to maximize the child’s ultimate functional independence and quality of life by minimizing the core autism spectrum disorder features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families.”  
• “Important issues, such as management of associated medical problems, pharmacologic and non-pharmacologic intervention for challenging behaviors or coexisting mental health conditions, and use of complementary and alternative medical treatments.” |
| **Carbone (2010)** | **Key points:**  
• “The earliest sign of autism in children is the delayed attainment of social skill milestones, including joint attention, social orienting, and pretend play. Language
impairment is a common, but less specific, sign of autism. Repetitive behaviors and restricted interests may not be noted until after social skill and communication impairments are exhibited. Physicians should perform developmental surveillance at all well-child visits", and especially between 18 and 24 months of age.

Reichow (Cochrane Review, 2012)  
Early Intensive Behavioral Intervention  
**Key points:**

- “There is some evidence that EIBI is an effective behavioral treatment for some children with ASD. However, the current state of the evidence is limited because of the reliance on data from non-randomized studies (CCTs) due to the lack of RCTs. Additional studies using RCT research designs are needed to make stronger conclusions about the effects of EIBI for children with ASD.”

Geretsegger (2014)  
Music therapy for patients with ASD  
**Key points:**

- Review of 10 studies with 165 participants.
- Music therapy may also help enhance nonverbal communication skills within the therapy context.
- Music therapy may contribute to increasing social adaptation skills in children with ASD.
- The application of music therapy requires specialized academic and clinical training.
- More studies are needed.

**Glossary**

**Comparative genomic hybridization (CGH)** — A technique for the detection of gains or losses in DNA copy number across the entire genome. CGH employs hybridization of differentially labeled tumor and reference DNA to create a map of DNA copy number changes in tumor genomes. Comparative genomic hybridization becomes a tool for analysis of chromosomal imbalances in archived tumor material and for examining possible correlations between these findings and tumor phenotypes.

**Early intensive behavioral intervention (EIBI)** — A type of applied behavior analysis (ABA) for very young children with ASD, usually younger than five and often younger than three.

**Fragile X syndrome** — Genetic condition that causes a range of developmental problems, including learning disabilities and cognitive impairment. Males are usually more severely affected by this disorder than females.

**Karyotype** — The number of chromosomes in a cell; 23 pairs in normal humans. Abnormalities are associated with Down, Turner and Klinefelter syndromes.

**References**

**Professional organizations:**


**Evidence-based reviews:**


**Clinical trials:**

Searched clinicaltrials.gov on July 23, 2015 using terms “autism” and “disorder” | Open Studies. 177 studies found, 1 relevant.


**CMS National Coverage Determinations (NCDs):**

No NCDs found for Autism Spectrum Disorder. CMS did commission a study on autism but it is on the Web, not in regulation. [http://www.hhs.gov/autism/factsheet_autism_support.html](http://www.hhs.gov/autism/factsheet_autism_support.html).

**Local Coverage Determinations (LCDs):**

No LCDs were found related to autism spectrum disorder.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants.</td>
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<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism variants for chromosomal abnormalities.</td>
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<tr>
<th>ICD-9 Code</th>
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<tr>
<td>299.00</td>
<td>Autistic disorder, current or active state.</td>
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<td>299.01</td>
<td>Autistic disorder, residual state.</td>
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<tr>
<td>299.80</td>
<td>Other specified pervasive developmental disorder, current or active state.</td>
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<tr>
<td>299.81</td>
<td>Other specified pervasive developmental disorder, residual state.</td>
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<tr>
<td>299.90</td>
<td>Unspecified pervasive developmental disorder, current or active state.</td>
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<tr>
<td>299.91</td>
<td>Unspecified pervasive developmental disorder, residual state.</td>
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<tr>
<td>ICD-10 Code</td>
<td>Description</td>
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<tr>
<td>F84.0</td>
<td>Autistic disorder</td>
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<tr>
<td>F84.5</td>
<td>Asperger's syndrome</td>
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<tr>
<td>F84.8</td>
<td>Other pervasive developmental disorders</td>
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<tr>
<td>F84.9</td>
<td>Pervasive developmental disorder, unspecified</td>
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<th>HCPCS Level II</th>
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