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: July 20, 2016
Next Review Date: July 2017

Related policies:

CP# 02.01.08  Familial polyposis gene testing
CP# 02.01.14  Gene expression profile testing for breast cancer
CP# 02.01.02  Genetic testing for breast and ovarian cancer
CP# 02.01.07  Genetic testing for cystic fibrosis
CP# 00.01.03  Genetic testing for cytochrome p450 Polymorphisms (CYP2C19)
CP# 05.01.03  Genetic testing for G1691A Polymorphisms Factor V Leiden
CP# 04.01.02  Genetic testing for Long QT syndrome (LQTS)
CP# 02.01.04  Genetic testing for primary autosomal recessive microcephaly
CP# 02.01.09  Genetic testing for rare diseases
CP# 13.01.01  Genetic testing for prostate cancer prognosis
CP# 09.01.09  Genetic testing in neurology
CP# 02.01.18  Genetic testing in sensorineural hearing loss
CP# 05.01.04  Molecular analysis for targeted therapy of non-small cell lung cancer
CP# 05.01.05  Molecular targeted therapy
CP# 02.01.03  Array comparative genomic hybridization testing

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’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 Keystone First 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. Keystone First’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. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.
**Coverage policy**

Keystone First considers the use of genetic testing for autism spectrum disorders (ASD) to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- There is clinical evidence of ASD meeting the criteria of the Diagnostic and Statistical Manual - Fifth Edition (American Psychiatric Association 2013).
- 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.

**Limitations:**

Keystone First considers the use of genetic testing for screening for ASD to be investigational and, therefore, not medically necessary.

The following tests will only be considered medically necessary when ordered by a specialist (e.g. geneticist, neurologist, or developmental pediatrician) and with documentation of appropriate genetic counseling

- 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).

All other uses of genetic testing for ASD to be investigational and, therefore, not medically necessary.

Note: The following CPT/HCPCS codes are not listed in the Pennsylvania Medicaid fee schedule:

81228 - Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants
Alternative covered services:

In-network visits to primary care physicians, behavioral health specialists, genetic counselors, as well as routine laboratory and radiographic, including magnetic resonance imaging (MRI), evaluations.

Background

ASD is considered to be a life-long condition impacting the affected individual’s capacity to communicate, interact socially and manage repetitive behaviors. Under 2013 revisions to the Diagnostic and Statistical Manual - Fifth Edition (American Psychiatric Association 2013) the criteria for consideration of ASD involve both communication disorders and a high degree of sensitivity to routine and repetitive behaviors (Appendix A).

ASD represents the phenotypic expression of a variety of pervasive neurologic and developmental delays (DD) and is not a singular diagnosis. Because it has a wide range of phenotypic expression, individuals may have significant impairment or be considered “high functioning” with the ability to function in modern society.

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. Typically, the manifestations of ASD become obvious in early childhood, but they may not become evident until later in childhood, adolescence or even adulthood.

Studies of ASD epidemiology have suggested multiple possible factors involved with the etiology of the condition. 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.

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 2014) or those who have exposures to pesticides (Shelton 2014). Others have looked at associations of post-traumatic stress disorders in mothers and ASD in their offspring (Roberts 2014).

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 to learn better coping skills and improve their innate capacity for integration into society. 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. 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 facilitate communication with educational and community resources.

**Searches**

Keystone First 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 21, 2016, 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 copy number variant (CNV) is a section (or sections) of the genome repeated once or multiple times over the length of the deoxyribonucleic acid (DNA) strand. The number of repeats in the genome varies between individuals in the human population. The discovery that CNVs — which can at times encompass large regions of DNA — are more common in patients with ASD has been the driver for the molecular diagnostic approach to identify this condition.

Historically, cytogenetic analysis (karyotyping) was performed to directly visualize chromosomes for any rearrangements, including gains and losses. However, in the modern era chromosomal microarray (CMA) technology has replaced cytogenetic analysis as a molecular diagnostic tool. CMA has greater resolution and can detect CNVs across the entire genome in a single test. CMA, as used here, encompasses all types of array-based genomic copy number analyses, including array-based comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays.

A comprehensive narrative review by Sun (2015) described first-tier diagnostic genetic tests for DDs. The authors described (but did not specifically recommend) a panoply of genetic tests including CMA. They posited that benefits of genetic testing include an improved sense of empowerment for patient families, refining treatment options, providing prognosis, preventing comorbidities, avoiding unnecessary
diagnostic tests, providing recurrence-risk-based counseling, and improving access to needed support or services. However, there was a paucity of evidence directly linking genetic testing to changes in health outcomes.

The major medical societies have referred to global developmental delay and intellectual disability as relatively common pediatric conditions and recommended genetic testing as a diagnostic approach based on published reports, mostly consisting of medium to large case series inclusive of these diagnostic tests.

Millichap (2014) wrote a recommended diagnostic approach to genetic testing for autism and other developmental deficits on behalf of the American Academy of Pediatrics (AAP):

CMA is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. Fragile X testing remains an important first-line test. The importance of considering testing for inborn errors of metabolism in this population is supported by a recent systematic review of the literature and several case series recently published. The role of brain MRI remains important in certain patients. The use of whole-genome testing is gaining popularity.

The American College of Medical Genetics (ACMG) has developed practice guidelines for the diagnosis of ASD that aim to improve the life of the affected individual (Schaefer 2013). The authors emphasize the importance of a "tiered" approach to the diagnostic evaluation. A full three-generation family history and pedigree analysis is recommended to identify known ASD-related syndromes or associated conditions:

- 22q11.2 deletions including velocardiofacial (Shprintzen) syndrome.
- Angelman syndrome.
- CHARGE syndrome.
- de Lange syndrome.
- Fragile X syndrome.
- MED12 disorders (including Lujan-Fryns syndrome).
- Prader-Willi syndrome.
- PTEN-associated disorders (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome).
- Rett syndrome.
- Smith-Lemli-Opitz syndrome.
- Smith-Magenis syndrome.
- Sotos syndrome.
- Tuberous sclerosis.
- PTEN, phosphatase and tensin.

The ACMG recommends that, in the presence of any of these syndromic presentations that genetic testing is indicated to identify a specific genetic cause and other comorbid conditions which may benefit
from treatment. According to ACMG such a strategy has improved the diagnostic yield of genetic testing for ASD from 6 — 12 percent to 30 — 40 percent. There are no published studies demonstrating clinical improvements in outcomes of children subjected to such testing; and unfortunately, there are no more than anecdotal reports whereby early initiation of behavioral health interventions, speech therapy and educational assistance have improved the lives of individuals with autism.

**Policy updates:**

In a narrative review Szego (2016) noted that an increasing number of relatively inexpensive and rapid testing methods are changing the landscape in the genetic diagnosis of ASD. Specifically, whole exome sequencing (WES) and whole genome sequencing (WGS) are being shown to increase the diagnostic yield when applied to patients suspected of having the condition. Exome sequencing is a technique for sequencing all the protein-coding genes in a genome (known as the exome). It consists of first selecting only the subset of DNA that encodes proteins (known as exons), and then sequencing that DNA using any high-throughput DNA sequencing technology. WGS incorporates the protein-encoding sections of the DNA plus those sections of the strand that are not directly involved with protein creation (e.g., regulatory genes within the strand).

The authors emphasize that WES and WGS do not obviate the use of CMA. Microarray testing itself is a high yield test identifying an etiology of ASD in about 10 percent of cases. Together WES and CMA in tandem may identify the cause of ASD in 20 percent of cases. As such, genome-wide testing has now joined CMA as a part of the standard diagnostic assessment for patients with ASD.

Tammimies (2015) tested 258 consecutively ascertained unrelated children with ASD who underwent detailed assessments to define morphology scores based on the presence of major congenital abnormalities and minor physical anomalies. The children were recruited between 2008 and 2013 in Newfoundland and Labrador, Canada. The probands were stratified into 3 groups of increasing morphological severity: essential, equivocal, and complex (scores of 0-3, 4-5, and ≥6). All probands underwent CMA, with WES performed for 95 proband-parent trios. Of 258 probands, 24 (9.3 percent, 95 percent CI, 6.1 — 13.5 percent) received a molecular diagnosis from CMA and 8 of 95 (8.4 percent, 95 percent CI, 3.7 — 15.9 percent) from WES. The yields were statistically different between the morphological groups. Among the children who underwent both CMA and WES testing, the estimated proportion with an identifiable genetic etiology was 15.8 percent (95 percent CI, 9.1 — 24.7 percent; 15/95 children). This included 2 children who received molecular diagnoses from both tests. The combined yield was significantly higher in the complex group when compared with the essential group (pairwise comparison, p = .002). The authors concluded that the molecular diagnostic yields of CMA and WES were comparable, and the combined molecular diagnostic yield was higher in children with more complex morphological phenotypes in comparison with the children in the essential category.

Siu (2016) writing for the United States Preventive Services Task Force (USPSTF) released in February the following statement with regard to screening children aged 18 to 30 months for ASD:
“The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for autism spectrum disorder (ASD) in young children for whom no concerns of ASD have been raised by their parents or a clinician.”

The AAP (2016) released the following statement with regard to the USPSTF recommendations:

“The AAP stands behind its recommendation that all children be screened for ASD at ages 18 and 24 months, along with regular developmental surveillance. This recommendation is encapsulated in the Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents, which serves as the blueprint for well-child visits and coverage under the Affordable Care Act. Health insurance coverage of ASD screening should not be impacted by the USPSTF statement.”

The American Academy of Family Physicians (AAFP) offered direction with the following clinical preventive service recommendation (2016):

“The AAFP concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician.”

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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</thead>
</table>
| Szego (2016) | **Key points:**  
• Narrative review noted that an increasing number of relatively inexpensive and rapid testing methods are changing the landscape in the genetic diagnosis of ASD.  
• WES and WGS increase the diagnostic yield when applied to patients suspected of having ASD.  
• CMA identifies an etiology of ASD in about 10 percent of cases.  
• Together WES and CMA may identify the cause of ASD in 20% of cases.  
• WGS and WES have now joined CMA as a part of the standard diagnostic assessment for patients with ASD. |
| Siu (2016) | **Key points:**  
• Policy statement with regard to screening children aged 18 to 30 months for ASD:  
  “The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician.” |
<table>
<thead>
<tr>
<th>Source</th>
<th>Key points:</th>
</tr>
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</table>
| AAP (2016)             | Policy statement with regard to the USPSTF recommendations:  
“The AAP stands behind its recommendation that all children be screened for ASD at ages 18 and 24 months, along with regular developmental surveillance. This recommendation is encapsulated in the Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents, which serves as the blueprint for well-child visits and coverage under the Affordable Care Act. Health insurance coverage of ASD screening should not be impacted by the USPSTF statement.” |
| AAFP (2016)            | Clinical preventive service recommendation:  
“The AAFP concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician.” |
All probands underwent CMA, with WES performed for 95 proband-parent trios.  
Of 258 probands, 24 (9.3%, 95%CI, 6.1% to 13.5%) received a molecular diagnosis from CMA  
Eight of 95 (8.4%, 95%CI, 3.7% to 15.9%) received a molecular diagnosis from WES.  
The yields were statistically different between the morphological groups.  
Among the children who underwent both CMA and WES testing, the estimated proportion with an identifiable genetic etiology was 15.8% (95%CI, 9.1% to 24.7%; 15/95 children).  
The combined yield was significantly higher in the complex group when compared with the essential group (pairwise comparison, P = .002). |
| Sun (2015)              | Technology assessment reviewed evidence for genetic testing in ASD.  
By test type, 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 DD genes has a yield of up to 42% in males with an appropriate family history. |
| Millichap (2014)        | “Chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology.”  
“The use of whole-exome sequencing as a diagnostic test is gaining popularity.” |
Geretsegger (2014)
Music therapy for people with autism spectrum disorder

Key points:
• Music therapy for patients with ASD 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.

Schaefer (2013)
Clinical Genetic Aspects of ASD Spectrum Disorders

Key points:
• 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.

Glossary

Autism spectrum disorders (ASD) — A collection of associated developmental disorders that affect the parts of the brain that control social interaction, verbal and non-verbal communication.

Chromosomal microarray analysis (CMA) — A diagnostic application suitable for evaluating individuals with unexplained developmental delay (DD), autism spectrum disease (ASD) or intellectual disability (intellectual developmental delay, mental retardation). It specifically looks for extra (duplicated) or missing (deleted) chromosomal segments, sometimes called copy number variants.

Copy number variant (CNV) — A phenomenon in which a section (or sections) of the genome is repeated once or multiple times over the length of the DNA strand. The number of repeats in the genome varies between individuals in the human population.

Fragile X syndrome — A 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.

Whole exome/genome sequencing (WES, WGS) — A technique for sequencing all the expressed genes in a genome (known as the exome). It is becoming a standard diagnostic tool for evaluating individuals
with unexplained developmental delay (DD), autism spectrum disease (ASD) or intellectual disability (intellectual developmental delay, mental retardation).

References

Professional society guidelines/others:


Peer-reviewed references:


Moeschler J, Shevell M. Clinical Genetic Evaluation of the Child With Mental Retardation or Developmental Delays. *Pediatr*. 2006;117(6); 2304 – 2316


**Clinical trials:**

Searched clinicaltrials.gov on June 21, 2016 using terms “autism” and “disorder” | Open Studies. 144 studies found, 2 relevant.


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

No NCDs were found at this time.

**Local Coverage Determinations (LCDs):**

No LCDs were found at this time.

**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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<tbody>
<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants.</td>
<td></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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<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>299.00</td>
<td>Autistic disorder, current or active state.</td>
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Appendix A.

### DSM-V criteria for the diagnosis of ASD

A. 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:

1. 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.

2. 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.

B. 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.

C. Restricted, repetitive patterns of behavior, interests or activities as manifested by two of the following:

1. Stereotyped or repetitive speech, motor movements or use of objects (e.g., simple motor stereotypies, echolalia, repetitive use of objects or idiosyncratic phrases).

2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change (e.g., motoric rituals, insistence on same route or food, repetitive questioning, or extreme distress at small changes).

3. Highly restricted, fixated interests abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment (e.g., 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).