Clinical Policy Title: Brain magnetic resonance imaging for autism

Clinical Policy Number: 09.01.15

Effective Date: May 1, 2017
Initial Review Date: April 19, 2017
Most Recent Review Date: April 19, 2017
Next Review Date: April 2018

Policy contains:
• Autism.
• Magnetic resonance imaging.

Related policies:

CP# 11.04.02 Genetic testing for autism spectrum disorders
CP# 02.01.24 Chromosomal microarray analysis

About this policy: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania'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 AmeriHealth Caritas Pennsylvania 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. AmeriHealth Caritas Pennsylvania’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. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of brain magnetic resonance imaging (MRI) for routine diagnosis and/or screening for autism spectrum disorders (ASD) to be investigational and, therefore, not medically necessary.

Alternative covered services:

In-network visits to primary care providers, behavioral health specialists, and genetic counselors, as well as routine diagnostic and follow-up laboratory and radiographic evaluations.

Background

ASD is a highly prevalent condition, estimated by the Centers for Disease Control (CDC 2016) at one in 68 persons, and is four times more common in males. Studies of ASD epidemiology have suggested multiple possible factors involved with the etiology of the condition, with a particular focus on
hereditary transmission. People with ASD are also more likely to have neurologic disorders, as ASD is among the more common neurobehavioral comorbidities of children with active epilepsy. Children with ASD are also 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 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).

ASD is considered to be a lifelong condition impacting the affected individual’s capacity to communicate, interact socially, and manage repetitive behaviors. Typically, the manifestations of ASD become obvious in early childhood, but they may not become evident until later in childhood, adolescence, or even adulthood.

Under 2013 revisions to the Diagnostic and Statistical Manual — Fifth Edition (DSM-5; American Psychiatric Association 2013), the criteria for diagnosis of ASD involve both communication disorders and aberrant behaviors (Appendix A).

The Affordable Care Act (ACA) mandates screening of young children at ages 18 to 24 months for ASD as part of the “essential health benefits” clause of the law, but there is no specific test identified to meet this mandate. In practice, this requirement is generally met by practitioners with a “well-child examination” that employs validated and standardized screening batteries.

Among the many available screening and diagnostic tools for general development and ASD are:

- Ages and Stages Questionnaire (ASQ).
- Communication and Symbolic Behavior Scale (CSBS).
- Parents’ Evaluation of Developmental Status (PEDS).
- Modified Checklist for Autism in Toddlers (MCHAT).
- Screening Tool for Autism in Toddlers and Young Children (STAT).
- Autism Diagnosis Interview — Revised (ADI-R).
- Autism Diagnostic Observation Schedule — Generic (ADOS-G).
- Childhood Autism Rating Scale (CARS).

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).
We conducted searches on January 30, 2017. Search terms were: “autism (MESH),” “brain MRI,” and “diagnosis of autism.”

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**

There is ample medical evidence of good quality to say that brain MRI can be an accurate tool in the diagnosis of ASD (Hazlett 2017; Yang 2016; Herringshaw 2016). However, its use as a routine diagnostic and/or screening modality presents practical issues (constraint of young children in the machine and emotional disturbance from the imaging suite environment and the device) and logistical constraints that diminish its viability. Less-intrusive and less time-consuming techniques of surveying for ASD (e.g., ASQ, ADI-R) offer a scientifically ethical and validated alternative to brain MRI as a screening and/or diagnostic tool in individuals young and old.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Hazlett (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Early brain development in infants at high risk for autism spectrum disorder</td>
<td>• Uncontrolled MRI neuroimaging trial of 106 infants considered at high familial risk (i.e., a sibling diagnosed with ASD) of ASD and 42 low-risk infants.</td>
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<td>• Authors noted hyperexpansion of the cortical surface area between 6 and 12 months of age precedes brain volume overgrowth observed between 12 and 24 months in 15 high-risk infants who were diagnosed with autism at 24 months.</td>
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<td>• Brain volume overgrowth was linked to the emergence and severity of autistic social deficits.</td>
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<td>• A deep-learning algorithm that primarily uses surface area information from magnetic resonance imaging of the brain of 6 – 12-month-old individuals predicted the diagnosis of autism in individual high-risk children at 24 months (with a positive predictive value of 81% and a sensitivity of 88%).</td>
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<td>• These findings demonstrate that early brain changes occur during the period in which autistic behaviors are first emerging.</td>
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<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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| Yang (2016) | **Key points:**  
- A systematic review and meta-analysis inclusive of thirteen studies.  
- Comparisons focused on brain changes in ASD and normal controls.  
- ASD individuals exhibited stronger effects in the anterior inferior parietal lobule, a part of the putative human mirror neuron system (MNS).  
- In addition, the ASD group demonstrated altered effects in the occipital cortex, dorsolateral prefrontal cortex, cingulate cortex, and insula.  
- These results suggest that ASD individuals demonstrate dysfunction of the MNS during action observation and imitation.  
- Furthermore, brain regions involved in visual processing, executive function, and social cognitive function might also show dysfunction during action task performance. |
| Herringshaw (2016) | **Key points:**  
- A systematic review and meta-analysis inclusive of 22 trials (n = 652).  
- Authors sought to quantify common and consistent patterns of brain activation during language processing in ASD and normal controls.  
- Within-group analysis showed largely overlapping patterns of language-related activation in both groups.  
- However, the ASD participants showed more right hemisphere activity in core language areas (i.e., superior temporal gyrus and inferior frontal gyrus), particularly in tasks where they had poorer performance accuracy; bilateral middle temporal gyrus (MTG) hypoactivation across many different paradigms; and increased activation of the left lingual gyrus in tasks where they had intact performance. |
| Siu (2016) | **Key points:**  
- Policy statement with regard to screening children ages 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." |
| AAP (2016) | **Key points:**  
- 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) | **Key points:**  
- Clinical preventive service recommendation: |
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<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>(Aged 18 to 30 Months)</td>
<td>“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.”</td>
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</table>
| Szego (2016) Whole Genome Sequencing as a Genetic Test for Autism Spectrum Disorder: From Bench to Bedside and then Back Again | **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.  
  - Whole exome sequencing (WES) and whole genome sequencing (WGS) increase the diagnostic yield when applied to patients suspected of having ASD.  
  - Chromosomal micro-array (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. |
| Blackmon (2015) Structural MRI biomarkers of shared pathogenesis in autism spectrum disorder and epilepsy | **Key points:**  
  - A narrative review noted that MRI studies demonstrate abnormal gray and white matter volumes present prior to onset of ASD.  
  - Typical findings include malformations of cortical development (MCDs), such as focal cortical dysplasia and heterotopias, which suggests disruption of neuronal migration as a contributing factor.  
  - The authors concluded that in vivo neuroimaging markers of subtle structural brain abnormalities could improve sample stratification in human clinical trials and potentially extend the range of patients that might benefit from treatment. |
| Tammimies (2015) Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with Autism Spectrum Disorder | **Key points:**  
  - Prospective study of 258 consecutive children with ASD between 2008 and 2013 in Newfoundland and Labrador, Canada.  
  - 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). |
| Conti (2015) The first 1000 days of the autistic brain: a systematic review of diffusion imaging studies | **Key points:**  
  - A systematic review inclusive of four trials reported higher fractional anisotropy values in subjects with ASD compared to controls within commissural fibers, projections fibers, and association fibers, suggesting brain hyper-connectivity in the earliest phases of the disorder.  
  - The authors proposed that a developmental course characterized by a shift toward
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<td><strong>Citation</strong></td>
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<td>Aoki (2015)</td>
<td>Neural bases of atypical emotional face processing in autism: A meta-analysis of fMRI studies</td>
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<td>• A systematic review undertook analysis of functional magnetic resonance imaging (fMRI) studies of whole brain analysis with emotional-face processing tasks in individuals with ASD.</td>
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<td>• Thirteen studies with 226 individuals with ASD and 251 typically developing people were identified.</td>
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<td>• The authors found ASD-related hyper-activation in subcortical structures, including bilateral thalamus, bilateral caudate, and right precuneus, and ASD-related hypo-activation in the hypothalamus during emotional-face processing.</td>
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<td>• Sub-analyses with more homogeneous contrasts preserved the findings of the main analysis, such as hyper-activation in sub-cortical structures (i.e., amygdala, hypothalamus and basal ganglia); moreover, the authors emphasized that hyper-activation of the left caudate was the most robust finding.</td>
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<td>DeRamus (2014)</td>
<td>Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders</td>
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<td>• A systematic review inclusive of 1,055 participants (506 ASD and 549 typically developing individuals) compared grey, white, and global differences in cortical matter between the groups.</td>
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<td>• Several findings were noted, including age-related decreases in grey and white matter in parietal and inferior temporal regions of the brain in ASD and age-related increases in grey matter in frontal and anterior-temporal regions.</td>
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<td>• The authors posited that the brains of individuals with ASD may have less-functional long-range (anterior-to-posterior) connections.</td>
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<td>Schaefer (2013)</td>
<td>Clinical Genetic Aspects of evaluation in identifying the etiology of autism spectrum disorders</td>
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<td>• All patients with ASDs should have a formal audiogram to rule out a significant hearing loss.</td>
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<td>• Role of the patient-centered medical home.</td>
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<td>• Referral for clinical genetics evaluation.</td>
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<td>• Tiered evaluation.</td>
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<td>• Genetic counseling.</td>
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<td>• Treatment and follow up.</td>
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<td>• A systematic review and meta-analysis on brain structure (277 ASD patients and 303 healthy controls) recognized six significant disturbances in the brain structure of ASD patients, including abnormalities in the lateral occipital lobe, the pericentral region, the medial temporal lobe, the basal ganglia, and proximate to the right parietal operculum.</td>
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<tr>
<td>Duerden (2012)</td>
<td>Regional differences in grey</td>
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| | • A systematic review and meta-analysis of 19 studies found common findings across age
and white matter in children and adults with autism spectrum disorders: an activation likelihood estimate (ALE) meta-analysis

groups were grey matter reduction in left putamen and medial prefrontal cortex (PFC) and grey matter increases in the lateral PFC, while white matter decreases were seen mainly in the children in frontostriatal pathways.

- In the ASD sample, children and adolescents were more likely than adults to have increased grey matter in bilateral fusiform gyrus, right cingulate, and insula.
- Results show that clear maturational differences exist in social cognition and limbic processing regions only in children and adolescents and not in adults with ASD and may underlie the emotional regulation that improves with age in this population.

Stanfield (2008)
Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies

Key points:

- Early attempts to find diagnostic MRI landmarks typical of autism were reviewed by Stanfield et al. as early as 2008.
- Attempting to sort the many structural brain abnormalities described in autism, the authors were confounded by studies that were often small and contradictory.
- In a seminal systematic study they categorized the results of previous analyses by age and IQ and found that total brain, cerebral hemispheres, cerebellum, and caudate nucleus sizes were increased in volume, whereas the corpus callosum area was reduced; moreover, there was evidence for a modifying effect of age and IQ on the cerebellar vermal lobules VI – VII and of age on the amygdala.
- The authors concluded that autism may result from abnormalities in specific brain regions and a global lack of integration due to brain enlargement, and that inconsistencies in the literature partly related to differences in the age and IQ of study populations.

References

Professional society guidelines/other:


**Peer-reviewed references:**


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

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**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>
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<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
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<td>70551</td>
<td>Magnetic resonance imaging, brain (including brainstem); without contrast material</td>
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<tr>
<td>70552</td>
<td>Magnetic resonance imaging, brain (including brainstem); with contrast</td>
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<tr>
<td>70553</td>
<td>Magnetic resonance imaging, brain (including brainstem); without contrast material, followed by contrast material(s) and further sequences</td>
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<tr>
<td>ICD-10 Code</td>
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<tr>
<td>F84.0</td>
<td>Autism disorder</td>
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<th>HCPCS Level II Code</th>
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**Appendix A**

**DSM-5 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.

3. 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.

**B.** 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).