

## Corporate Medical Policy

### Testing for Autism Spectrum Disorder and Developmental Delay AHS – M2176 “Notification”

**File Name:** testing\_for\_autism\_spectrum\_disorder\_and\_developmental\_delay  
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#### Description of Procedure or Service

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##### Description

Autism spectrum disorder (ASD) is a complex condition typically associated with deficits in social interaction and communication, as well as restrictive and repetitive behaviors and sensory issues (Ivanov, Stoyanova, Popov, & Vachev, 2015; Persico, Ricciardello, & Cucinotta, 2019). ASD is typically identified in early childhood (Lord, Elsabbagh, Baird, & Veenstra-Vanderweele, 2018; Persico et al., 2019) and has multiple etiologies, sub-types, and developmental trajectories (Masi, DeMayo, Glozier, & Guastella, 2017). Intellectual disability, attention deficit hyperactivity disorder, and epilepsy are commonly seen in children with ASD (Augustyn, 2020). Further, ASD is known to have a strong genetic component and is diagnosed in all racial, ethnic, and socioeconomic groups (Ivanov et al., 2015; Lord et al., 2018).

Note: For guidance regarding testing for *FMR1* mutations or Rett syndrome, please refer to the following policies: Genetic Testing for FMR1 Mutations AHS-M2028 and Genetic Testing for Rett Syndrome AHS-M2088, respectively.

##### Related Policies

[Whole Genome and Whole Exome Sequencing AHS – M2032](#)

[Chromosomal Microarray AHS – M2033](#)

[Genetic Testing for FMR1 Mutations AHS – M2028](#)

[Genetic Testing for Rett Syndrome AHS – M2088](#)

[Genetic Testing for PTEN Hamartoma Tumor Syndrome AHS – M2087](#)

[Genetic Testing for CHARGE Syndrome AHS – M2070](#)

[Genetic Testing for Epilepsy AHS – M2075](#)

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

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**BCBSNC will provide coverage for testing for testing for autism spectrum disorder and developmental delay when it is determined the medical criteria or reimbursement guidelines below are met.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Testing for Autism Spectrum Disorder and Developmental Delay is covered

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1. Targeted genetic testing of a child with signs and symptoms of Autism Spectrum Disorder (ASD) or developmental delay (See Notes 1) is considered medically necessary as follows:
  - a. If syndrome diagnosis or metabolic disorder is suspected based on physical examination (such as dysmorphology, growth parameters [including head circumference], and skin examination), the appropriate targeted testing must be ordered.

Note 1: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please see Laboratory Procedures Reimbursement Policy AHS – R2162

## When Testing for Autism Spectrum Disorder and Developmental Delay is not covered

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1. Multi-gene panel testing of more than 50 genes on a single platform is considered not medically necessary.
2. Concurrent ordering of multi-gene panel tests for a specific condition (e.g. ASD) is considered not medically necessary; only one multi-gene panel test may be ordered at a time for a specific condition.
3. Testing for carbon metabolites and/or amines, including but not limited to melatonin, serotonin, and amino acids, in any body fluid is considered not medically necessary to screen for or diagnose either ASD or non-ASD developmental delay.
4. MicroRNA (miRNA) analysis in any body fluid is considered not medically necessary to screen for or diagnose either ASD or non-ASD developmental delay.

Microbiome analysis in any body fluid is considered not medically necessary to screen for or diagnose either ASD or non-ASD developmental delay.

## Policy Guidelines

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### Background

Autism spectrum disorder (ASD) is a prevalent neurodevelopmental disorder affecting approximately one in 45 children in the United States with an average male to female ratio of 4–5:1; very similar ASD prevalence rates are reported around the world (Vuong & Hsiao, 2017; Wiśniowiecka-Kowalik & Nowakowska, 2019). ASD is typically characterized by impaired social interaction and other restrictive and repetitive behaviors, and ASD is diagnosed behaviorally based on the presence of abnormal social communication and repetitive behavior (Vuong & Hsiao, 2017).

The condition may be either idiopathic or syndromic, with many syndromic cases related to genetic disorders, such as Rett syndrome (Persico et al., 2019). While many aspects relating to the etiology of the condition are poorly understood, ASD is known to have a strong genetic component; many familial inheritance patterns have been associated with the condition, and up to

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1000 genes may be potentially implicated (Ramaswami & Geschwind, 2018). Known ASD risk factors include chromosomal deletion(s) and prematurity (R. A. Muhle, Reed, Stratigos, & Veenstra-VanderWeele, 2018). Researchers report that parents who have a child with autism have a 2-18% chance of having another child with autism (Lyll et al., 2017; Waye & Cheng, 2018).

Diagnosis of ASD includes a comprehensive evaluation by a multidisciplinary team to determine if the child’s symptoms meet the criteria for ASD, as outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), to determine the child’s neurodevelopment profile of strengths and weaknesses, and to assess whether the child has any other associated or underlying condition(s) (Augustyn & von Hahn, 2020). The fifth edition of the DSM requires the individual have all of the following:

- Social communication and social interaction deficits in multiple settings as demonstrated by all of the following—social-emotional reciprocity, a lack of understanding or awareness of the feelings of others; nonverbal communicative behaviors; difficulty in developing, maintaining, and understanding interpersonal relationships; and
- Repetitive behavior patterns as demonstrated with at least two of the following—stereotyped or repetitive movements; obsessive, compulsive adherence to routines or patterns of verbal or nonverbal behaviors; highly fixated, abnormal preoccupation on specific interests; increased or decreased responses to sensory input, such as adverse responses to environment; and
- Impaired function due to symptoms; and
- Symptoms present early in developmental period of life; and
- Symptoms “are not better explained by intellectual disability (formerly referred to as mental retardation) or global developmental delay (Augustyn & von Hahn, 2020).”

A differential diagnosis of ASD from other conditions that impair social communication, interaction, or development may help guide possible therapeutic options. These conditions include both global delay (or intellectual disability) and intellectual giftedness, social communication disorder, developmental language disorder, learning disorders, hearing impairment, Landau-Kleffner syndrome (LKS or acquired epileptic aphasia), Rett syndrome, fetal alcohol spectrum disorder (FASD), attachment disorder, attention deficit hyperactivity disorder (ADHD), anxiety disorder, obsessive-compulsive disorder (OCD), stereotypic movement disorder, or tic disorders (such as Tourette syndrome). Each of these disorders may share individual characteristics of ASD while exhibiting distinguishing characteristics for their respective condition, such as appropriate imaginative play, normal reciprocal social interactions, or specific morphologies (e.g. the characteristic facial features of FASD) (Augustyn & von Hahn, 2020; Hyman, Levy, & Myers, 2020; Volkmar et al., 2014).

Both genetic and environmental factors play a part in the etiology of ASD. Even though ASD is more prevalent in males, male-to-male transmission in certain lineages indicates that ASD is not solely X-linked (Hallmayer et al., 1996; R. Muhle, Trentacoste, & Rapin, 2004). Genetic analysis can be performed using chromosomal microarray, karyotype, or genetic sequencing including next-generation sequencing (NGS) or whole exome sequence (WES) analysis. Specific genetic testing should be based on the clinical findings of the affected individual and family history. The American College of Medical Genetics and Genomics reports “the following approximate diagnostic yields are expected in the genetic evaluation of ASDs:

- CMA [chromosomal microarray] (10%)

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- Fragile X (1-5%)
- *MECP2* (4% of females)
- *PTEN* (5% of those with head circumferences >2.5 SDs [standard deviations] that are tested)
- Karyotype (3%)
- Other (10%). Currently, there are no published studies that collate the yield on the other identifiable etiologies of autism... Using empiric estimates and clinical experience, this has been estimated as 10% (Schaefer & Mendelsohn, 2013).”

Chromosomal microarray (CMA) is a microarray-based genomic copy-number analysis test that can be used to help diagnose unexplained developmental delay, intellectual disability, and ASD, as well as multiple congenital anomalies (Miller et al., 2010). CMA cannot detect balanced translocations; however, these de novo translocations are infrequently encountered (Beaudet, 2013). Karyotype can be used in instances where a balanced translocation is suspected, such as a history of two or more miscarriages (Augustyn & von Hahn, 2020).

Besides CMA and karyotyping, genetic sequencing can be used to screen for possible mutations, in particular NGS and WES analysis. NGS refers to the use of a single platform to sequence multiple strands of nucleic acid rapidly in parallel. This technique can be utilized to screen the entire exome for whole exome sequencing (or WES) analysis (Hulick, 2020). A number of genetic tests are commercially available, including the Clarifi™ test (Quadrant Biosciences, Inc.), an NGS-based saliva test that measures epigenetic microRNAs and the microbiome to generate an algorithmic report of the predictive probability of ASD (Quadrant\_Biosciences, 2020a, 2020b).

While it is believed that inborn errors of metabolism account for only 5% of autistic individuals, defects in one-carbon metabolism are one of the most-often reported physiopathologies reported to be associated with autism, as these disturbances to cellular bioenergetics lead to increased oxidative stress, impaired redox homeostasis, and methylation disruption, the third of which portend to deficits in gene expression, neurotransmitter synthesis, and neuronal synchronization (Carrasco, Salazar, Tiznado, & Ruiz, 2019; Paşca et al., 2009). Similarly, with regard to amines, neurotransmitters that are amino acids and their derivatives are thought to play critical roles in the diagnosis of ASD, with hypotheses ranging from the differentiation and migration of neurons, the synaptic plasticity of neurons, and the perturbation of reward- and motivation-related circuits modulated by concentrations of serotonin, glutamate, and dopamine, respectively (Pavāl, 2017; Vargason et al., 2018). It is no surprise, then, that the richness of the field means that it is ripe for a foray into expanding our understanding of ASD and the concomitant therapeutic consequences.

In addition to genetic testing, different biomarkers have been proposed as possible aids in diagnosing ASD and developmental delay. The Children’s Autism Metabolome Project (CAMP) [Clinical Trials Identifier NCT02548442], funded by a grant from the National Institutes of Mental Health (NIMH) and sponsored by Stemina Biomarker Discovery, Inc., has a goal to identify metabolic signature profiles in blood plasma and/or urine that can differentiate children with ASD from children with either non-ASD delayed development or typical development. CAMP, expected to be completed in 2023, is a multi-center clinical study at eight sites within the United States that has more than 1100 enrolled participants as of 2020 (NeuroPointDx, 2020a; NLM, 2020). To date, the focus has been on amino acid metabolism dysregulation. Stemina Biomarker Discovery, Inc. does offer commercially available biomarker tests for ASD, including the NeuroPointDX Autism Spectrum Disorder (NPDX ASD) blood test, that measures 32 different amines present in blood plasma using LC-MS/MS. Then, a proprietary algorithm based on the ADOS-2 reference method indicates the individual’s metabolic subtype (or “metabotype”). For example, in a positive metabotype 3 profile “indicate[s] a positive metabolic profile associated with ASD. The imbalance detected indicates an increase in concentration of Glycine relative to the concentration of Asparagine (NeuroPointDx, 2020b)”.

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## Clinical Validity and Utility

Tammimies et al. (2015) compared the molecular diagnostic yield of CMA and whole exome sequencing (WES) in children (n = 258) with ASD, split into three groups based on severity of morphology (essential, equivocal, and complex). They note that 15.8% of the children who underwent both CMA and WES testing have an identifiable genetic etiology. Statistical differences between the three morphological groups were recorded, and the “combined yield was significantly higher in the complex group when compared with the essential group (pairwise comparison,  $P = .002$ ).” Individually, CMA and WES produced similar yields; for example, 4.2% of children in the essential group tested positive with CMA as compared to 3.1% undergoing WES. The authors conclude that “the molecular diagnostic yields of CMA and WES were comparable... If replicated in additional populations, these findings may inform appropriate selection of molecular diagnostic testing for children affected by ASD (Tammimies et al., 2015).” Rossi et al. (2017) performed a study of WES on 163 individuals with either ASD or autistic features, reporting that 61.9% of positive findings were de novo mutations. Moreover, individuals “presenting with psychiatric conditions or ataxia or paraplegia in addition to autism spectrum disorder or autistic features were significantly more likely to receive positive results compared with patients without these clinical features (95.6% vs 27.1%,  $P < 0.0001$ ; 83.3% vs 21.2%,  $P < 0.0001$ , respectively) (Rossi et al., 2017).”

Ragusa et al. (2020) evaluated 53 ASD children who were treatment-naïve and 27 unaffected controls by performing miRNA expression profiling and 16S rRNA microbiome analysis on saliva samples. Their results show an upregulation of miR-29a-3p and miR-141-3p and downregulation of miR-16-5p, miR-let-7b-50, and mi-R-451a in children with ASD. “Microbiome analysis on the same subjects revealed that *Rothia*, *Filifactor*, *Actinobacillus*, *Weeksellaceae*, *Ralstonia*, *Pasteurellaceae*, and *Aggregatibacter* increased their abundance in ASD patients, while *Tannerella*, *Moryella* and *TM7-3* decreased (Ragusa et al., 2020).”

Hicks et al. (2018) performed a multi-center, cross-sectional validation study of the Clarifi™ test (Quadrant Biosciences, Inc.) using children aged 19 – 83 months. The individuals were divided among three groups: a control, neurotypical group (n=134); a group with a diagnosis of ASD (n=238); and a group with non-ASD developmental delay (n=84). Randomly, prior to initiating the study, all individuals were further divided between the training and independent validation sets (82% and 18%, respectively). The training set established the RNA-based algorithm to be used to distinguish ASD and non-ASD children while the validation set was used to test the algorithm accuracy. Using the established algorithm from the training set, the authors state that the validation test “maintained an AUC of 0.88 (82% sensitivity and 88% specificity). Notably, the RNA features were implicated in physiologic processes related to ASD (axon guidance, neurotrophic signaling) (Hicks et al., 2018).” These data further supported their earlier findings from a smaller study (n=45) that 14 miRNAs “were differentially expressed in ASD subjects compared to controls ( $p < 0.05$ ; FDR  $< 0.15$ ) and showed more than 95 % accuracy at distinguishing subject groups in the best-fit logistic regression model (Hicks, Ignacio, Gentile, & Middleton, 2016).”

Hicks et al. (2020) also performed a multi-center study to use saliva microRNAs to differentiate children with ASD (n=187) from peers with typical (n=125) or non-ASD atypical development (n=69). 14 miRNAs showed differential expression, and four miRNAs “best differentiated children with ASD from children without ASD in training (area under the curve = 0.725) and validation (area under the curve = 0.694) sets. Eight microRNAs were associated ( $R > 0.25$ , false discovery rate  $< 0.05$ ) with social affect, and 10 microRNAs were associated with restricted/repetitive behavior.” The authors conclude, “Salivary microRNAs are “altered” in children with ASD and associated with levels of ASD behaviors. Salivary microRNA collection is noninvasive, identifying ASD-status with moderate accuracy. A multi-‘omic’ approach using additional RNA families could improve accuracy, leading to clinical application (Hicks et al., 2020).”

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László, Horváth, Eck, and Fekete (1994) reported that not only were the mean values of serotonin for autistic children higher as compared to the control group— 1.253  $\mu\text{mol/l}$  and 0.88  $\mu\text{mol/l}$ , respectively—but also that hyperserotonemia was detected in 20 of the 46 autistic children, corroborating a previous report of elevated levels of serum serotonin in 40% of affected children (László et al., 1994). The study also noted that in 20% (n=30) of patients lactic acidosis and hyperpyruvatemias were detected in the absence of hyperserotonemia, urging that these metabolites be explored as important targets for managing infantile autism (László et al., 1994).

A Seoul National University Bandung Hospital study that recruited 59 subjects afflicted by ASD—sorted into the affected group—and their unaffected family members (both biological parents and unaffected siblings), who comprised the unaffected group of 135 members provides greater evidence for the use of mitochondrial markers in the diagnosis of ASD (Oh, Kim, & Yoo, 2020). The measuring of carbon metabolites demonstrated that not only did the affected group boast significantly higher lactate than the unaffected group (19.79  $\pm$  11.29 vs. 13.84  $\pm$  6.12 mg/dl at  $p < 0.01$ ) but also had higher lactate-to-pyruvate ratios (21.47  $\pm$  18.43 vs. 15.03  $\pm$  9.37 at  $p < 0.05$ ); however, what was strange was that there were no significant correlations between the parameters themselves (Oh et al., 2020). This supports previous findings that reported elevated lactate and lactate-to-pyruvate ratios in ASD individuals, and further corroborates the notion that defects in mitochondria can lead to and potentially explain neurodevelopmental disorders for their roles in both aerobic energy production and the development of neurons in the CNS (Oh et al., 2020; Paşca et al., 2009).

Moreover, another study focusing on the profile of metabolic abnormalities expected due to mitochondrial dysfunction demonstrated that in a sample of 146 Egyptian boys (73 autistic, 73 unaffected), plasma levels of lactate and serum pyruvate, lactate-to-pyruvate ratio, creatine kinase, pyruvate kinase, and LDH (glycolytic enzyme expression) were significantly higher ( $p < 0.05$ ) among the subjects than in the unaffected control group, while amines such as serum L-carnitine (participating in the beta-oxidation of fatty acids) and urea were in turn lower, save for ammonia (Hassan, Desoky, Sakhr, Gabra, & Bakri, 2019). Interestingly, blood levels of all previously measured biochemical markers did not differ between mild to moderately autistic children as compared to those severely impacted except for significantly higher oxidative stress index and significantly lower antioxidant levels, suggesting that the ASD is not explicable by a singular etiology (Hassan et al., 2019).

However, though the testing of any one metric for the diagnosis of ASD seems untenable and wasteful, the use of many measurements operating in conjunction has gained traction. Dysregulation of amino acid metabolism was identified by comparing plasma metabolites from 516 children with ASD with a control group of 164 typical-development children recruited into Children’s Autism Metabolome Project (CAMP) (Smith et al., 2019). Though a simple analysis of the mean concentrations of free plasma amines did not reveal meaningful differences between the ASD and healthy populations of children, the researchers reported that a combination of glutamine, glycine, and ornithine amino acid dysregulation ‘metabotypes’ could be used to identify a dysregulation in amino acid/branch-chained amino acid metabolism that is present in 16.7% of the CAMP ASD subjects and is detectable with a specificity of 96.3% and a PPV of 93.5%, seemingly providing the grounds for metabolic testing (Smith et al., 2019).

Arizona State University’s Comprehensive Nutritional and Dietary Intervention Study, a 12-month nutritional and dietary intervention study, compared plasma amino acid concentrations between ASD and typically developed individuals. 64 study participants were on the autism spectrum and 49 acted as age- and gender-matched typical-development (TD) controls. In the clinical study, a total of 42 plasma amino acids and related metabolites were measured, including the 9 essential and 11 non-essential amino acids as well as 22 secondary amino acids and amino acid metabolites (Vargason et al., 2018). However, even given the comprehensiveness of the study, at most could be said was that the results “indicate possibly elevated concentrations of

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glutamate, hydroxyproline, and serine in the plasma of individuals with ASD’ but ultimately that “clear discrimination of the cohorts [ASD and TD cohorts] was not possible using these data”, suggesting that the measurements themselves are less significant than previously anticipated (Vargason et al., 2018). However, a 2011 study in Arizona analyzed concentrations of 41 amino acids and amino acid metabolites in the plasma of 55 children with ASD and 44 TD children and detected significantly elevated glutamate and significantly decreased tryptophan in the ASD cohort (Adams et al., 2011). Similarly, a 2016 Chinese study reported that glutamate in the plasma of 51 children with ASD and 51 controls were significantly higher in the children with ASD consistent with the Arizona study (Cai, Ding, Zhang, Xue, & Wang, 2016). Therefore, aside from a singular common amino acid, the findings contradict other studies focusing on plasma amino acid measurements in ASD individuals that exalt and exhort it for its purported potential.

## **Guidelines and Recommendations**

### **American Academy of Pediatrics (AAP) (Hyman et al., 2020)**

In 2020, the American Academy of Pediatrics released extensive guidelines pertaining to the identification, evaluation, and management of children with ASD. The AAP notes, “The reported prevalence of children with ASD has increased over time... This increase may be attributable to several factors, including broadening in the diagnostic criteria with ongoing revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the more inclusive definition of pervasive developmental disorder with the adoption of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) in 1994, increased public awareness of the disorder and its symptoms, recommendations for universal screening for ASD, and increased availability of early intervention and school-based services for children with ASD.” The AAP goes on to explicitly recommend “screening all children for symptoms of ASD through a combination of developmental surveillance at all visits and standardized autism-specific screening tests at 18 and 24 months of age in their primary care visits because children with ASD can be identified as toddlers, and early intervention can and does influence outcomes. This autism-specific screening complements the recommended general developmental screening at 9, 18, and 30 months of age.” They also recommend the use of the “Learn the Signs. Act Early” parent resources developed by the Centers for Disease Control and Prevention (CDC). Screening varies by age group, and screening results are not diagnostic. The results are to aid the primary care provider in identifying children who may require additional evaluation. For children younger than 18 months, the M-CHAT is the most studied tool, and the AAP notes that parent-administered questionnaires, such as the Communication and Symbolic Behavior Scales Development Profile and the Infant and Toddler Checklist, have been used to screen children as young as 12-months old. For children 18- to 30-months old, the most used screening tool is either the M-CHAT or M-CHAT-R/F (Modified Checklist for Autism in Toddlers, Revised with Follow-Up Questions). For children older than 30 months, “there are no validated screening tools available for use in pediatric practice, nor are there current recommendations by the AAP for universal screening for ASD in that age group (Hyman et al., 2020).”

Once a child has been determined to be at risk for ASD, the child should see a specialist, such as a neurodevelopmental or developmental/behavioral pediatrician, psychologist, neurologist, or a psychiatrist for a diagnostic evaluation. “At this time, there are no laboratory tests that can be used to make a diagnosis of ASD, so careful review of the child’s behavioral history and direct observation of symptoms are necessary... Formal assessment of language, cognitive, and adaptive abilities and sensory status is an important component of the diagnostic process (Hyman et al., 2020).” The specialist may use questionnaire tools, such as the SCQ or Social Responsiveness Scale (SRS), or behavioral assessments, such as the Diagnostic Interview for Social and Communication Disorders (DISCO) or Child Behavior Checklist.

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Concerning genetic testing, the AAP states that “[g]enetic evaluation should be recommended and offered to all families as part of the etiologic workup”, and they provide a stepwise general approach as a practical guideline.

1. “Consider referral for pediatric genetics evaluation
2. Comprehensive history (including 3-generation family history with emphasis on individuals with ASD and other developmental, behavioral and/or psychiatric, and neurologic diagnoses)
  - a. Physical examination (including dysmorphology, growth parameters [including head circumference], and skin examination)
    - i. If syndrome diagnosis or metabolic disorder is suspected, go back to step 1 (genetics and/or metabolism referral) and/or order the appropriate targeted testing)
    - ii. Otherwise, proceed to step 3
3. Laboratory studies
  - a. Discuss and offer CMA analysis
  - b. Discuss and offer fragile X analysis; if family history is suggestive of sex-linked intellectual disabilities, refer to genetics for additional testing
  - c. If a patient is a girl, consider evaluation for Rett syndrome, MECP2 testing
  - d. If these studies do not reveal the etiology, proceed to step 4
4. Consider referral to genetics, workup might include WES (Hyman et al., 2020).”

Regarding the use of potential biomarkers for ASD, AAP states, “Although some studies have attempted to differentiate people with and without ASD on the basis of differences in laboratory profiles of platelet serotonin, plasma melatonin, urine melatonin sulfate, redo status, placental trophoblast inclusions, and immune function, currently no diagnostic laboratory tests have been approved for ASD. To date, none of these potential biomarkers under study has sufficient evidence to be recommended (Hyman et al., 2020).” AAP also notes, “The yield of routine metabolic testing for children with ASD is low and not recommended for regular use.” However, they do note that there are uncommon metabolic disorders that may “rarely” be associated with ASD that may require necessary work-up. These can include metabolic disorders involving amino acids, carnitine, folate, and cholesterol, for example.

## **U.S. Preventive Services Task Force (USPSTF) (Siu et al., 2016)**

The USPSTF, in 2016, concluded “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 (Siu et al., 2016).” Within this evaluation, the USPSTF did not address either genetic testing or the potential use of biomarkers for screening ASD.

## **The International Standard Cytogenomic Array (ISCA) Consortium (Miller et al., 2010)**

In 2010, the ISCA released a consensus statement that chromosomal microarray is a first-tier diagnostic test for individuals with developmental disabilities and delays, including individuals with ASD. The ISCA “strongly supports the use of CMA in place of G-banded karyotyping as the first-tier cytogenetic diagnostic test for patients with DD/ID, ASD, or MCA. G-banded karyotype analysis should be reserved for patients with obvious chromosomal syndromes (e.g. Down syndrome), a family history of chromosomal rearrangement, or a history of multiple miscarriages (Miller et al., 2010).”

## **American Academy of Child and Adolescent Psychiatry (AACAP) (Volkmar et al., 2014)**

Within the 2014 AACAP guidelines, they recommend that “clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD... All children with ASD should

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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 (Volkmar et al., 2014).”

## **American Academy of Neurology (AAN, 2014)**

The AAN reaffirmed their guidelines in 2014. They recommend developmental surveillance on all children during well-child visits from infancy through school-age (Level B). They recommend the use of the Ages and States Questionnaire, the BRIGANCE® Screens, the Child Development Inventories, and the Parents’ Evaluations of Developmental Status (Level B). With a Level B recommendation, they do not recommend the use of the following tools: the Denver-II (DDST-II) and the Revised Denver Pre-Screening Developmental Questionnaire (R-DPDQ). Under laboratory investigations, with a Level B recommendation, they recommend lead screening for any child with developmental delay and pica with periodic screening should pica persist. With a Level A recommendation, they recommend genetic testing in children with ASD, “specifically high resolution chromosome studies (karyotype) and DNA analysis for FraX [fragile X], should be performed in the presence of mental retardation (or if mental retardation cannot be excluded), if there is a family history of FraX or undiagnosed mental retardation, or if dysmorphic features are present... However, there is little likelihood of positive karyotype or FraX testing in the presence of high-functioning autism (AAN, 2014).”

Concerning metabolic testing, the AAN gives a Level A recommendation for “selective metabolic testing” that “should be initiated by the presence of suggestive clinical and physical findings such as the following: if lethargy, cyclic vomiting, or early seizures are evident; the presence of dysmorphic or coarse features; evidence of mental retardation or if mental retardation cannot be ruled out; or if occurrence or adequacy of newborn screening at birth is questionable.” However, they do not go into greater detail regarding specific metabolic testing. They do give the following Level B recommendation: “There is inadequate supporting evidence for hair analysis, celiac antibodies, allergy testing (particularly food allergies for gluten, casein, candida, and other molds), immunologic or neurochemical abnormalities, micronutrients such as vitamin levels, intestinal permeability studies, stool analysis, urinary peptides, mitochondrial disorders (including lactate and pyruvate), thyroid function tests, or erythrocyte glutathione peroxidase studies (AAN, 2014).”

## **Centers for Disease Control and Prevention (CDC, 2019)**

The CDC website for recommendations and guidelines for ASD supports the guidelines of the American Academy of Pediatrics (AAP) and the American Academy of Neurology (also supported by the Child Neurology Society).

## **American College of Medical Genetics and Genomics (ACMG) (Schaefer & Mendelsohn, 2013)**

Within the 2013 ACMG guidelines, they recommend that a genetic consultation be offered to all individuals with ASD as well as their families. They also recommend the use of a tiered genetic diagnostic evaluation, consisting of the following:

- “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

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- 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 male patients only)<sup>a</sup>
- 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)

<sup>a</sup>DNA testing for fragile X in females if indicators present (e.g., family history and phenotype) (Schaefer & Mendelsohn, 2013).”

## National Institute for Health and Care Excellence (NICE, 2017)

Concerning genetic testing in the NICE guidelines, they state, “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: genetic tests, as recommended by your regional genetics centre, if there are specific dysmorphic features, congenital anomalies and/or evidence of a learning (intellectual) disability.... (NICE, 2017)”

## Applicable Federal Regulations

A search of the FDA device database on 10/21/2020 using the term “autism” yielded 0 results. Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81470, 81471, 0063U, 0139U, 0170U*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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## Policy Implementation/Update Information

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- 2/9/21 New policy developed. BCBSNC will provide coverage for testing for autism spectrum disorder and developmental delay when it is determined to be medically necessary because the medical criteria and guidelines are met. Policy noticed 2/9/21, effective 4/20/21. Medical Director review 1/2021. (jd)

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