LOUISIANA BLUE

avalon

Testing for Developmental Delay

Policy Number: AHS – M2176 – Testing for Developmental Delay	Original Effective Date: 05/015/2022 Archival Date: 05/01/2026

POLICY DESCRIPTION | RELATED POLICIES | INDICATIONS AND/OR LIMITATIONS OF COVERAGE | TABLE OF TERMINOLOGY | SCIENTIFIC BACKGROUND | GUIDELINES AND RECOMMENDATIONS | APPLICABLE STATE AND FEDERAL REGULATIONS | APPLICABLE CPT/HCPCS PROCEDURE CODES | EVIDENCE-BASED SCIENTIFIC REFERENCES | REVISION HISTORY

I. Policy 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 et al., 2015; Persico et al., 2019). ASD is typically identified in early childhood (Lord et al., 2018; Persico et al., 2019) and has multiple etiologies, subtypes, and developmental trajectories (Masi et al., 2017). Intellectual disability, attention deficit hyperactivity disorder, and epilepsy are commonly seen in children with ASD (Augustyn, 2024). 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).

II. Related Policies

Policy Number	Policy Title
N/A	Not Applicable

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

1) For the diagnosis of autism spectrum disorder (ASD) or non-syndromic developmental delay, all other testing outside of chromosomal microarray, whole exome sequencing, or whole genome sequencing or genetic testing for fragile X syndrome or Rett syndrome **DOES NOT MEET COVERAGE CRITERIA**.

IV. Table of Terminology

Term	Definition
AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ACMG	American College of Medical Genetics and Genomics

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Archived

ADHD	Attention deficit hyperactivity disorder
ADOS-2	Autism diagnostic observation schedule
ASD	Autism spectrum disorder
AUC	Area under the curve
CAMP	Children's Autism Metabolome Project
CDC	Centers for Disease Control and Prevention
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMA	Chromosomal microarray
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CNVs	Copy number variants
DD	Developmental disability
DISCO	Diagnostic interview for social and communication disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
FASD	Fetal alcohol spectrum disorder
FDA	Food and Drug Administration
FMR1	*Fragile X messenger ribonucleoprotein 1*
ID	Intellectual disability
IQ	Intelligence quotient
ISCA	International standard cytogenomic array
LC-MS/MS	Liquid chromatography–mass spectrometry/mass spectrometry
LDH	Lactate dehydrogenase
LDT	Laboratory-developed test
LKS	Landau-Kleffner syndrome
MCA	Multiple congenital anomalies
M-CHAT	Modified Checklist for Autism in Toddlers
M-CHAT-R/F	M-CHAT, revised with follow-up questions
MECP2	*Methyl-CpG binding protein 2*
miRNA	Micro ribonucleic acid
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NIMH	National Institutes of Mental Health
OCD	Obsessive-compulsive disorder
PRS	Polygenic risk scores
PTEN	*Phosphatase and tensin homolog*
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
SCQ	Social communication questionnaire
SCZ	Schizophrenia
SDs	Standard deviations
SNP	Single-nucleotide polymorphisms

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

SRS	Social responsiveness scale
TD	Typical development
USPSTF	United States Preventive Services Task Force
WES	Whole exome sequencing

V. Scientific Background

Autism spectrum disorder (ASD) is a prevalent neurodevelopmental disorder affecting approximately one in 36 children in the United States (CDC, 2024b). 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 1000 genes may be potentially implicated (Ramaswami & Geschwind, 2018). Known ASD risk factors include chromosomal deletion(s) and prematurity (Muhle et al., 2018). Researchers report that parents who have a child with autism have a 2-18% chance of having another child with autism (Lyall 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, 2024). The fifth edition of the DSM requires the individual have all 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, 2024).

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

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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, 2024; Hyman et al., 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 (Muhle et al., 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%)
- 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, 2024).

Besides CMA and karyotyping, genetic sequencing can be used to screen for possible mutations, specifically 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 WES analysis (Hulick, 2024). 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, 2024).

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 et al., 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 (Pavăl, 2017; Vargason et al., 2018). It is no surprise, then, that the richness of

Archived

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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, 2024a; 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 three 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, 2024b).

Xiaoxiao et al. (2023) conducted a plasma proteomic and metabolomic study of 122 children with ASD. Participants were divided into three groups: a group of children that had risk genes (de novo mutations), ASD children without risk genes, and a healthy control group. After plasma proteomics and metabolomics analyses, the authors found "the protein or metabolism profile of the children with or with no risk genes was more clustered and overlapped, with a separation trend from the control." In ASD children, most complement pathway proteins were upregulated, and the authors noted specifically the complement pathway proteins: "C2, CPB2, IGHV3-74, and IGHV5051," were upregulated, "supporting the notion that autistic patients may experience complement activation in their peripherals" (Xiaoxiao et al., 2023).

Clinical Utility and Validity

Tammimies et al. (2015) compared the molecular diagnostic yield of CMA and 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).

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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 to 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 et al., 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). In total, 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).

László et al. (1994) reported that not only were the mean values of serotonin for autistic children higher as compared to the control group– 1.253 µmol/l and 0.88 µmol/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 hyperpyruvatemia 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 with 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 evidence for the use of mitochondrial markers in the diagnosis of ASD (Oh et al., 2020). The measuring of carbon metabolites demonstrated that not only did the affected group boast significantly higher lactate than the unaffected group (19.79 ± 11.29 vs. 13.84 ± 6.12 mg/dl at $p<0.01$) but also had higher lactate-to-pyruvate ratios (21.47 ± 18.43

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

vs. 15.03 ± 9.37 at $p<0.05$); however, 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).

A 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 et al., 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).

Although 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 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. The study included 64 study participants 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 nine 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 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 et al., 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.

Archived

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

LaBianca et al. (2021) conducted a study on the relation between copy number variants (CNVs) and polygenic risk scores (PRS) on the extent of care needed for families with histories of autism and/or ADHD. They estimated that among a sample of 39 families, the overall variance explained by "known, rare, CNVs and SCZ [schizophrenia] PRS from common SNP [single nucleotide polymorphisms] to be 10% in comorbid ASD and ADHD." There was also a greater burden of both rare CNVs and SCZ PRS among adult ASD and/or ADHD patients with sustained needs of specialist care than unaffected relatives and any other relatives with mental health disorder. Although the study had a small sample size, having this application of CNVs and PRS can eventually predict care and benefit other families with ASD and/or ADHD, as well as assist in clinical decision making. Furthermore, CNV can be connected to autistic phenotypes. In a study by Chawner et al. (2021), they found that based on clinical cut-offs, four different genetic variant groups had differences in autism severity, IQ, and autism subdomain profiles, with a "substantial variability in phenotypic outcome within individual genetic variant groups" (74%-97%), with low variability between groups (1%-21% based on trait). For carriers, 54% with one of four CNVs that did not meet "full autism diagnostic criteria" still had "elevated levels of autistic traits." Collectively, these studies demonstrate that not only can CNVs render predictive value in treatment planning, but also understanding of presentation.

Genetic testing also yields pathogenic benefit. In a retrospective chart review by Harris et al. (2020) on 500 toddlers diagnosed with ASD per the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, 59.8% completed genetic testing, with 12.0% yielding pathogenic findings from CMA and fragile X testing. The most common CNVs in this sample were "deletions or duplications on 15q (n=10) and 22q (n=2). Among subjects with fragile X findings, there were 3 full mutations, 3 pre mutations, 2 intermediate or "grey zone" mutations, and 1 patient with mosaicism." These pathogenic findings also impacted medical recommendations 72.2% of those patients, showing how understanding pathogenesis in the setting of ASD can extend into not only identifying potential pathology but also clinical care once again. Bruno et al. (2021) used WES to investigate parent-offspring trios. The study included 60 trios, each of which included a patient (diagnosed with ASD or an ID-related phenotype) and their parents. The authors found eight pathogenic variants already known to be associated with ASD and ID (*SYNGAP1, SMAD6, PACS1, SHANK3, KMT2A, KCNQ2, ACTB,* and *POGZ*). The authors also found four novel candidate ASD/ID genes with de novo disruptive variants (*MBP, PCDHA1, PCDH15, PDPR).* The authors conclude that "these unknown rare variants, alone or in combination with each other, contributed to the phenotype." Further, the authors conclude that "data confirm the efficacy of WES in detecting pathogenic variants in known and novel ID/ASD genes" (Bruno et al., 2021).

Harrington et al. (2024) studied the ordering habits of providers to assess the diagnostic utility of genetic testing for ASD. The authors included data from a "large clinical laboratory" that was collected between 2017 and 2022. The authors found that females were 1.4 times more likely than males to receive a genetic diagnosis of ASD (95% CI:1.2-1.7). Overall, "exome had the highest diagnostic yield (24.5%), followed by NDD panel (6.4%), CMA (6.2%), and Fragile X testing (0.4%)." The authors concluded that "ASD testing should include exome, CMA, and other clinically indicated tests, as first-tier tests, with the consideration of panel testing, in cases where exome sequencing is not an option" (Harrington et al., 2024).

VI. Guidelines and Recommendations

American Academy of Pediatrics (AAP)

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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 Developmental 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.

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)

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

   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 workup. These can include metabolic disorders involving amino acids, carnitine, folate, and cholesterol, for example (Hyman et al., 2020).

U.S. Preventive Services Task Force (USPSTF)

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. This guideline is currently being updated as of June 4, 2021.

The International Standard Cytogenomic Array (ISCA) Consortium

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)

Within the 2014 AACAP guidelines, they recommend that "clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD… All children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray" (Volkmar et al., 2014).

Centers for Disease Control and Prevention (CDC)

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

The CDC website for recommendations and guidelines for ASD supports the guidelines of the AAP (CDC, 2024a).

American College of Medical Genetics and Genomics (ACMG)

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
    - 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)[a]
- 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 imagining only in the presence of specific indicators (e.g., microcephaly, regression, seizures, and history of stupor/coma)

  [a]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)

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, 2021).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Archived

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
0063U	Neurology (autism), 32 amines by LC-MS/MS, using plasma, algorithm reported as metabolic signature associated with autism spectrum disorder Proprietary test: NPDX ASD ADM Panel I Lab/Manufacturer: Stemina Biomarker Discovery, Inc
0263U	Neurology (autism spectrum disorder [ASD]), quantitative measurements of 16 central carbon metabolites (i.e., α-ketoglutarate, alanine, lactate, phenylalanine, pyruvate, succinate, carnitine, citrate, fumarate, hypoxanthine, inosine, malate, S-sulfocysteine, taurine, urate, and xanthine), liquid chromatography tandem mass spectrometry (LC-MS/MS), plasma, algorithmic analysis with result reported as negative or positive (with metabolic subtypes of ASD) Proprietary test: NPDX ASD and Central Carbon Energy Metabolism Lab/Manufacturer: Stemina Biomarker Discovery, Inc
0322U	Neurology (autism spectrum disorder [ASD]), quantitative measurements of 14 acyl carnitines and microbiome-derived metabolites, liquid chromatography with tandem mass spectrometry (LC-MS/MS), plasma, results reported as negative or positive for risk of metabolic subtypes associated with ASD Proprietary test: NPDX ASD Test Panel III Lab/Manufacturer: Stemina Biomarker Discovery d/b/a NeuroPointDX

Current Procedural Terminology© American Medical Association. All Rights reserved.

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

Adams, J. B., Audhya, T., McDonough-Means, S., Rubin, R. A., Quig, D., Geis, E., Gehn, E., Loresto, M., Mitchell, J., Atwood, S., Barnhouse, S., & Lee, W. (2011). Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. *Nutr Metab (Lond)*, *8*(1), 34. https://doi.org/10.1186/1743-7075-8-34

Augustyn, M. (2024). *Autism spectrum disorder: Terminology, epidemiology, and pathogenesis*. Retrieved 10/17/2023 from https://www.uptodate.com/contents/autism-spectrum-disorder-in-children-and-adolescents-terminology-epidemiology-and-pathogenesis

Augustyn, M., & von Hahn, L. E. (2024). *Autism spectrum disorder: Evaluation and diagnosis*. Retrieved 10/17/2023 from https://www.uptodate.com/contents/autism-spectrum-disorder-in-children-and-adolescents-evaluation-and-diagnosis

Beaudet, A. L. (2013). The utility of chromosomal microarray analysis in developmental and behavioral pediatrics. *Child Dev*, *84*(1), 121-132. https://doi.org/10.1111/cdev.12050

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Bruno, L. P., Doddato, G., Valentino, F., Baldassarri, M., Tita, R., Fallerini, C., Bruttini, M., Lo Rizzo, C., Mencarelli, M. A., Mari, F., Pinto, A. M., Fava, F., Fabbiani, A., Lamacchia, V., Carrer, A., Caputo, V., Granata, S., Benetti, E., Zguro, K., . . . Ariani, F. (2021). New Candidates for Autism/Intellectual Disability Identified by Whole-Exome Sequencing. *Int J Mol Sci*, *22*(24). https://doi.org/10.3390/ijms222413439

Cai, J., Ding, L., Zhang, J. S., Xue, J., & Wang, L. Z. (2016). Elevated plasma levels of glutamate in children with autism spectrum disorders. *Neuroreport*, *27*(4), 272-276. https://doi.org/10.1097/wnr.0000000000000532

Carrasco, M., Salazar, C., Tiznado, W., & Ruiz, L. M. (2019). Alterations of Mitochondrial Biology in the Oral Mucosa of Chilean Children with Autism Spectrum Disorder (ASD). *Cells*, *8*(4), 367. https://doi.org/10.3390/cells8040367

CDC. (2024a). *Autism Spectrum Disorder (ASD)*. Centers for Disease Control and Prevention. https://www.cdc.gov/autism/

CDC. (2024b). *Data and Statistics on Autism Spectrum Disorder*. https://www.cdc.gov/autism/data-research/

Chawner, S. J. R. A., Doherty, J. L., Anney, R. J. L., Antshel, K. M., Bearden, C. E., Bernier, R., Chung, W. K., Clements, C. C., Curran, S. R., Cuturilo, G., Fiksinski, A. M., Gallagher, L., Goin-Kochel, R. P., Gur, R. E., Hanson, E., Jacquemont, S., Kates, W. R., Kushan, L., Maillard, A. M., . . . van den Bree, M. B. M. (2021). A Genetics-First Approach to Dissecting the Heterogeneity of Autism: Phenotypic Comparison of Autism Risk Copy Number Variants. *The American journal of psychiatry*, *178*(1), 77-86. https://doi.org/10.1176/appi.ajp.2020.20010015

Harrington, C. N., Morales, A., Bernstein, J. A., & Calderwood, L. (2024). Implications of Provider Specialty, Test Type, and Demographic Factors on Genetic Testing Outcomes for Patients with Autism Spectrum Disorder. *J Autism Dev Disord*. https://doi.org/10.1007/s10803-024-06423-1

Harris, H. K., Sideridis, G. D., Barbaresi, W. J., & Harstad, E. (2020). Pathogenic Yield of Genetic Testing in Autism Spectrum Disorder. *Pediatrics*, *146*(4), e20193211. https://doi.org/10.1542/peds.2019-3211

Hassan, M. H., Desoky, T., Sakhr, H. M., Gabra, R. H., & Bakri, A. H. (2019). Possible Metabolic Alterations among Autistic Male Children: Clinical and Biochemical Approaches. *Journal of Molecular Neuroscience*, *67*(2), 204-216. https://doi.org/10.1007/s12031-018-1225-9

Hicks, S. D., Carpenter, R. L., Wagner, K. E., Pauley, R., Barros, M., Tierney-Aves, C., Barns, S., Greene, C. D., & Middleton, F. A. (2020). Saliva MicroRNA Differentiates Children With Autism From Peers With Typical and Atypical Development. *J Am Acad Child Adolesc Psychiatry*, *59*(2), 296-308. https://doi.org/10.1016/j.jaac.2019.03.017

Hicks, S. D., Ignacio, C., Gentile, K., & Middleton, F. A. (2016). Salivary miRNA profiles identify children with autism spectrum disorder, correlate with adaptive behavior, and implicate ASD candidate genes involved in neurodevelopment. *BMC Pediatr*, *16*, 52. https://doi.org/10.1186/s12887-016-0586-x

Hicks, S. D., Rajan, A. T., Wagner, K. E., Barns, S., Carpenter, R. L., & Middleton, F. A. (2018). Validation of a Salivary RNA Test for Childhood Autism Spectrum Disorder. *Front Genet*, *9*, 534. https://doi.org/10.3389/fgene.2018.00534

Hulick, P. (2024, September 14). *Next-generation DNA sequencing (NGS): Principles and clinical applications*. https://www.uptodate.com/contents/next-generation-dna-sequencing-ngs-principles-and-clinical-applications

Hyman, S. L., Levy, S. E., & Myers, S. M. (2020). Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics*, *145*(1). https://doi.org/10.1542/peds.2019-3447

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Ivanov, H. Y., Stoyanova, V. K., Popov, N. T., & Vachev, T. I. (2015). Autism Spectrum Disorder - A Complex Genetic Disorder. *Folia Med (Plovdiv)*, *57*(1), 19-28. https://doi.org/10.1515/folmed-2015-0015

LaBianca, S., LaBianca, J., Pagsberg, A. K., Jakobsen, K. D., Appadurai, V., Buil, A., & Werge, T. (2021). Copy Number Variants and Polygenic Risk Scores Predict Need of Care in Autism and/or ADHD Families. *J Autism Dev Disord*, *51*(1), 276-285. https://doi.org/10.1007/s10803-020-04552-x

László, A., Horváth, E., Eck, E., & Fekete, M. (1994). Serum serotonin, lactate and pyruvate levels in infantile autistic children. *Clinica Chimica Acta*, *229*(1-2), 205-207. https://doi.org/10.1016/0009-8981(94)90243-7

Lord, C., Elsabbagh, M., Baird, G., & Veenstra-Vanderweele, J. (2018). Autism spectrum disorder. *Lancet*, *392*(10146), 508-520. https://doi.org/10.1016/s0140-6736(18)31129-2

Lyall, K., Croen, L., Daniels, J., Fallin, M. D., Ladd-Acosta, C., Lee, B. K., Park, B. Y., Snyder, N. W., Schendel, D., Volk, H., Windham, G. C., & Newschaffer, C. (2017). The Changing Epidemiology of Autism Spectrum Disorders. *Annu Rev Public Health*, *38*, 81-102. https://doi.org/10.1146/annurev-publhealth-031816-044318

Masi, A., DeMayo, M. M., Glozier, N., & Guastella, A. J. (2017). An Overview of Autism Spectrum Disorder, Heterogeneity and Treatment Options. *Neurosci Bull*, *33*(2), 183-193. https://doi.org/10.1007/s12264-017-0100-y

Miller, D. T., Adam, M. P., Aradhya, S., Biesecker, L. G., Brothman, A. R., Carter, N. P., Church, D. M., Crolla, J. A., Eichler, E. E., Epstein, C. J., Faucett, W. A., Feuk, L., Friedman, J. M., Hamosh, A., Jackson, L., Kaminsky, E. B., Kok, K., Krantz, I. D., Kuhn, R. M., . . . Ledbetter, D. H. (2010). Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*, *86*(5), 749-764. https://doi.org/10.1016/j.ajhg.2010.04.006

Muhle, R., Trentacoste, S. V., & Rapin, I. (2004). The genetics of autism. *Pediatrics*, *113*(5), e472-486. https://doi.org/10.1542/peds.113.5.e472

Muhle, R. A., Reed, H. E., Stratigos, K. A., & Veenstra-VanderWeele, J. (2018). The Emerging Clinical Neuroscience of Autism Spectrum Disorder: A Review. *JAMA Psychiatry*, *75*(5), 514-523. https://doi.org/10.1001/jamapsychiatry.2017.4685

NeuroPointDx. (2024a). *Autism Clinical Studies*. https://neuropointdx.com/studies/

NeuroPointDx. (2024b). *Understanding NPDX ASD Test Results*. Retrieved 10/17/2023 from https://neuropointdx.com/providers/understanding-the-results/

NICE. (2017, 12/20/2017). *Autism spectrum disorder in under 19s: recognition, referral and diagnosis*. National Institue for Health and Care Excellence. Retrieved 10/05/2020 from https://www.nice.org.uk/guidance/cg128/chapter/Recommendations

NICE. (2021). *Autism spectrum disorder in adults: diagnosis and management*. https://www.nice.org.uk/guidance/cg142/chapter/Recommendations

NLM. (2020, 06/29/2020). *ClinicalTrials.gov: Children's Autism Metabolome Project (CAMP-01)*. Retrieved 10/21/2020 from https://clinicaltrials.gov/ct2/show/NCT02548442

Oh, M., Kim, S. A., & Yoo, H. J. (2020). Higher Lactate Level and Lactate-to-Pyruvate Ratio in Autism Spectrum Disorder. *Exp Neurobiol*, *29*(4), 314-322. https://doi.org/10.5607/en20030

Paşca, S. P., Dronca, E., Kaucsár, T., Crăciun, E. C., Endreffy, E., Ferencz, B. K., Iftene, F., Benga, I., Cornean, R., Banerjee, R., & Dronca, M. (2009). One carbon metabolism disturbances and the C677T MTHFR gene polymorphism in children with autism spectrum disorders. *Journal of Cellular and Molecular Medicine*, *13*(10), 4229-4238. https://doi.org/10.1111/j.1582-4934.2008.00463.x

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Pavăl, D. (2017). A Dopamine Hypothesis of Autism Spectrum Disorder. *Developmental Neuroscience*, *39*(5), 355-360. https://doi.org/10.1159/000478725

Persico, A. M., Ricciardello, A., & Cucinotta, F. (2019). The psychopharmacology of autism spectrum disorder and Rett syndrome. *Handb Clin Neurol*, *165*, 391-414. https://doi.org/10.1016/b978-0-444-64012-3.00024-1

Quadrant Biosciences. (2024). *Clarifi(tm): Healthcare Providers*. Quadrant Biosciences, Inc. Retrieved 10/17/2023 from https://quadrantbiosciences.com/

Ragusa, M., Santagati, M., Mirabella, F., Lauretta, G., Cirnigliaro, M., Brex, D., Barbagallo, C., Domini, C. N., Gulisano, M., Barone, R., Trovato, L., Oliveri, S., Mongelli, G., Spitale, A., Barbagallo, D., Di Pietro, C., Stefani, S., Rizzo, R., & Purrello, M. (2020). Potential Associations Among Alteration of Salivary miRNAs, Saliva Microbiome Structure, and Cognitive Impairments in Autistic Children. *Int J Mol Sci*, *21*(17). https://doi.org/10.3390/ijms21176203

Ramaswami, G., & Geschwind, D. H. (2018). Genetics of autism spectrum disorder. *Handb Clin Neurol*, *147*, 321-329. https://doi.org/10.1016/b978-0-444-63233-3.00021-x

Rossi, M., El-Khechen, D., Black, M. H., Farwell Hagman, K. D., Tang, S., & Powis, Z. (2017). Outcomes of Diagnostic Exome Sequencing in Patients With Diagnosed or Suspected Autism Spectrum Disorders. *Pediatr Neurol*, *70*, 34-43.e32. https://doi.org/10.1016/j.pediatrneurol.2017.01.033

Schaefer, G. B., & Mendelsohn, N. J. (2013). Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med*, *15*(5), 399-407. https://doi.org/10.1038/gim.2013.32

Siu, A. L., Bibbins-Domingo, K., Grossman, D. C., Baumann, L. C., Davidson, K. W., Ebell, M., García, F. A., Gillman, M., Herzstein, J., Kemper, A. R., Krist, A. H., Kurth, A. E., Owens, D. K., Phillips, W. R., Phipps, M. G., & Pignone, M. P. (2016). Screening for Autism Spectrum Disorder in Young Children: US Preventive Services Task Force Recommendation Statement. *Jama*, *315*(7), 691-696. https://doi.org/10.1001/jama.2016.0018

Smith, A. M., King, J. J., West, P. R., Ludwig, M. A., Donley, E. L. R., Burrier, R. E., & Amaral, D. G. (2019). Amino Acid Dysregulation Metabotypes: Potential Biomarkers for Diagnosis and Individualized Treatment for Subtypes of Autism Spectrum Disorder. *Biol Psychiatry*, *85*(4), 345-354. https://doi.org/10.1016/j.biopsych.2018.08.016

Tammimies, K., Marshall, C. R., Walker, S., Kaur, G., Thiruvahindrapuram, B., Lionel, A. C., Yuen, R. K., Uddin, M., Roberts, W., Weksberg, R., Woodbury-Smith, M., Zwaigenbaum, L., Anagnostou, E., Wang, Z., Wei, J., Howe, J. L., Gazzellone, M. J., Lau, L., Sung, W. W., . . . Fernandez, B. A. (2015). Molecular Diagnostic Yield of Chromosomal Microarray Analysis and Whole-Exome Sequencing in Children With Autism Spectrum Disorder. *Jama*, *314*(9), 895-903. https://doi.org/10.1001/jama.2015.10078

Vargason, T., Kruger, U., McGuinness, D. L., Adams, J. B., Geis, E., Gehn, E., Coleman, D., & Hahn, J. (2018). Investigating Plasma Amino Acids for Differentiating Individuals with Autism Spectrum Disorder and Typically Developing Peers. *Res Autism Spectr Disord*, *50*, 60-72. https://doi.org/10.1016/j.rasd.2018.03.004

Volkmar, F., Siegel, M., Woodbury-Smith, M., King, B., McCracken, J., & State, M. (2014). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*, *53*(2), 237-257. https://doi.org/10.1016/j.jaac.2013.10.013

Vuong, H. E., & Hsiao, E. Y. (2017). Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder. *Biol Psychiatry*, *81*(5), 411-423. https://doi.org/10.1016/j.biopsych.2016.08.024

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Waye, M. M. Y., & Cheng, H. Y. (2018). Genetics and epigenetics of autism: A Review. *Psychiatry Clin Neurosci*, *72*(4), 228-244. https://doi.org/10.1111/pcn.12606

Xiaoxiao, T., Feng, C., Zhao, Y., Zhang, H., Gao, Y., Cao, X., Hong, Q., Lin, J., Zhuang, H., Feng, Y., Wang, H., & Shen, L. (2023). A study of genetic heterogeneity in autism spectrum disorders based on plasma proteomic and metabolomic analysis: multiomics study of autism heterogeneity. *MedComm*, *2023*, e380. https://doi.org/10.1002/mco2.380

X. Review/Revision History

Effective Date	Summary
05/01/2026	Clinical Advisory Board Meeting, policy review and approval: 12/03/2025 Policy Archived
04/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: Title changed from "Testing for Autism Spectrum Disorder and Developmental Delay" to "Testing for Developmental Delay" CC1 edited for clarity, now reads: "1) For individuals less than 18 years of age who have had a physical examination suggestive of syndromic developmental delay or developmental delay due to a metabolic disorder (e.g., dysmorphology, growth parameters [including head circumference], skin examination), targeted genetic testing MEETS COVERAGE CRITERIA." CC2 edited to reflect that all other tests other than types addressed in other policies (CMA, WES, WGS, FXS, RTT) are not appropriate for ASD or non-syndromic developmental delay, moves below disclaimer about testing not meeting criteria due to a lack of scientific support. Now reads: "2) For the diagnosis of autism spectrum disorder (ASD) or non-syndromic developmental delay, all other testing outside of chromosomal microarray, whole exome sequencing, or whole genome sequencing or genetic testing for fragile X syndrome or Rett syndrome DOES NOT MEET COVERAGE CRITERIA." Note was updated to reflect changes to Avalon's definition of a genetic panel within R2162. Now reads: "Note: For two or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy." Client requested variance: Remove CC1, "For individuals less than 18 years of age who have had a physical examination suggestive of syndromic developmental delay or developmental delay due to a metabolic disorder (e.g., dysmorphology, growth parameters [including head circumference], skin examination), targeted genetic testing MEETS COVERAGE CRITERIA." Remove Note 1, "Note: For two or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy." Add 0322U.
07/01/2024	Client requested variance: removal of codes 81470, 81471, and 0170U
05/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity:

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

	With this, results in changes to CC1, which was edited (resulting in deletion of Notes 2-4) to reflect that targeted testing is for suspected syndromic developmental delay or developmental delay due to a suspected metabolic condition. CC2 edited for clarity that the 50 gene panel limitation is specific to the diagnosis of autism spectrum disorder (ASD) or developmental delay Note 1 is now a general note for the policy, now reads: "Note: For 5 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy."
03/10/2023	Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: All coverage criteria edited for clarity and consistency. What were previously CC4-6 are now a single criteria with 3 subcriteria, CC4a-c, as all are types of tests not meeting CC for screening/diagnosing ASD/non-ASD developmental delay. Client requested variance: Add "(See Note 1 below)" to CC1.
05/15/2022	Initial Policy Implementation

Archived

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield Association.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.