



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders is addressed separately in medical policy 00389.

Note: Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss is addressed separately in medical policy 00449.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider chromosomal microarray analysis (CMA) as first-line testing to be **eligible for coverage**** in the initial evaluation of individuals with any of the following:

- Apparently nonsyndromic developmental delay/intellectual disability (DD/DI); or
- Autism spectrum disorder (ASD); or
- Multiple congenital anomalies not specific to a well-delineated genetic syndrome

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

Based on review of available data, the Company considers panel testing using next-generation sequencing (NGS) in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability, autism spectrum disorder, or congenital anomalies to be **investigational**.*

Based on review of available data, the Company considers chromosomal microarray for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay to be **investigational**.*

Policy Guidelines

Use of CMA testing as outlined in this policy is not intended for use in the prenatal period.

A guidelines update from American College of Medical Genetics (Schaefer et al [2013]) stated that a stepwise (or tiered) approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first tier to include fragile X syndrome and CMA testing.

Recommendations from the American College of Medical Genetics (Manning and Hudgins [2010]) on array-based technologies and their clinical utilization for detecting chromosomal abnormalities include the following: “Appropriate follow-up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH [fluorescent in situ hybridization] studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.”

In some cases of CMA analysis, the laboratory performing the test confirms all reported copy number variants with an alternative technology, such as fluorescent in situ hybridization analysis.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Diagnostic Testing

Karyotyping and Fluorescent In Situ Hybridization

The goal of a cytogenetic evaluation is to identify chromosomal imbalances that cause a disorder. The most common imbalances are copy number variants (CNVs) or deletions and duplications of large segments of genomic material. CNVs are common in developmental delay /intellectual disability and ASD but more often reflect the normal genetic variation. However, de novo CNVs are observed about 4 times more frequently in children with ASD than in normal individuals. Less frequently, other abnormalities such as balanced translocations (ie, exchanges of equally sized DNA loci between chromosomes) may be pathogenic. For many well-described syndromes, the type and location of the associated chromosomal abnormality have been established by studying large patient samples. For others, few patients with similar abnormalities may have been evaluated to establish genotype-phenotype correlation. Finally, in some patients, the cytogenetic analysis will discover chromosomal abnormalities that require study to determine their significance.

Prior to the advent of CMAs, the initial step in the cytogenetic analysis was G-banded karyotyping, which evaluates all chromosomes. High-resolution G-banding can detect changes as small as 3 to 5 megabases in size, although standard G-banding evaluates more than 10 megabases changes. In children with developmental delay/intellectual disability, a review by Stankiewicz and Beaudet (2007) found G-banded karyotyping diagnostic in approximately 3% to 5% of cases. In ASD, high-resolution karyotyping appears to identify abnormalities in up to 5% of cases.

In contrast, molecular cytogenetic techniques can detect small submicroscopic chromosomal alterations. Fluorescent in situ hybridization (FISH), a targeted approach, is used to identify specific chromosomal abnormalities associated with suspected diagnoses such as DiGeorge syndrome. Prior to CMAs, FISH was also used to screen the rearrangement-prone subtelomeric regions. Subtelomeric FISH was found to identify abnormalities in children with developmental delay and intellectual

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

disability, diagnostic in approximately 5% to 6% of those with negative karyotypes, but uncommonly in ASD.

Chromosomal Microarrays

Two types of CMAs are considered here: array comparative genomic hybridization (aCGH) and single nucleotide variants (SNV) arrays. The aCGH approach uses DNA samples from a patient and normal control. Each is labeled with distinct fluorescent dyes (red or green). The labeled samples are then mixed and hybridized to thousands of cloned or synthesized reference (normal) DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions simultaneously. CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. If the patient sequence is missing part of the normal sequence (a deletion) or has the normal sequence plus additional genomic material within that genomic location (eg, a duplication), the sequence imbalance is detected as a difference in fluorescence intensity (Korf and Rehm [2013] offers an illustrative graphic). For this reason, aCGH cannot detect balanced chromosomal translations (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base-pair order) because the fluorescence intensity would not change. A portion of the increased diagnostic yield from CMA over karyotyping comes from the discovery that chromosomal rearrangements that appear balanced (and therefore not pathogenic) by G-banded karyotype analysis are found to have small imbalances with greater resolution. It has been estimated that 40% of apparently balanced de novo or inherited translocations with abnormal phenotype are associated with cryptic deletion if analyzed by CMA testing.

Like aCGH, SNV arrays detect CNVs. In an SNV array, the 2 alleles for genes of interest are tagged with different fluorescent dyes. Comparative fluorescence intensity will be increased when there are duplications and diminished with deletions. The resolution provided by aCGH is higher than with SNV arrays. In addition, aCGH has better signal-to-background characteristics than SNV arrays. In contrast to aCGH, SNV arrays will also identify long stretches of DNA homozygosity, which may suggest uniparental disomy or consanguinity. Uniparental disomy occurs when a child inherits 2 copies of a chromosome from 1 parent and no copies from the other parent. Uniparental disomy can lead to syndromes such as Angelman and Prader-Willi.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

Table 1 summarizes the cytogenetic tests used to evaluate children with developmental delay/intellectual disability and autism. The table emphasizes the large difference in resolution between karyotyping and CMA.

Table 1. Resolution and Analysis Comparison of FISH, Karyotyping, and CMA Analysis

Test	Resolution in Kilobases ^a	Analysis
Karyotyping	3000-5000 kb	Genome-wide
CMA	≈50 kb	Genome-wide
FISH	≈500 to 1000 kb (depending on probe)	Targeted

CMA: chromosomal microarray; FISH: fluorescent in situ hybridization; kb: kilobases.

^a 1 kb = 1000 bases, 1000 kb = 1 Mb.

Microarrays may be prepared by the laboratory using the technology or, more commonly, by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of laboratory-developed and commercially available platforms prompted the American College of Medical Genetics to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.

Next-Generation Sequencing

Next-generation sequencing has been proposed to detect single-gene causes of autism and possibly identify a syndrome that involves autism in patients with normal array-based testing. Next-generation sequencing involves the sequencing of millions of fragments of genetic material in a massively parallel fashion. Next-generation sequencing can be performed on segments of the genetic material of various sizes $\frac{3}{4}$ from the entire genome (whole-genome sequencing) to small subsets of genes (targeted sequencing). Next-generation sequencing allows the detection of SNVs, CNVs, insertions, and deletions. With higher resolution comes a higher likelihood of detection of variants of uncertain significance.

Genetic Associations With Developmental Delay/Intellectual Disability and Autism Spectrum Disorder

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

For common phenotypes and syndromes, the pathogenicity of CNVs may be supported by considerable evidence; for uncommon phenotypes and uncommon CNVs determining pathogenicity requires a systematic evaluation that includes parental studies, examining databases for reported associations, and considering the molecular consequences of the identified variant. Parental studies (eg, “trio” testing of affected child, father, and mother) can identify an inherited CNV from an unaffected parent and therefore considered benign. A variety of databases index the clinical implications of CNVs and their associations with a particular phenotype. CNVs are continuously cataloged and, with growth in CMA testing and improved resolution, databases have become increasingly extensive (eg, DECIPHER, ClinVar). For uncommon CNVs, in addition to reports of CNV-phenotype associations, the location and size of the CNV can offer clues to pathogenicity; larger CNVs are more often pathogenic and the role of affected genes in brain circuitry and effect of CNV on gene expression can implicate pathogenicity. Although uncommon, an observed phenotype can result from unmasking a mutated recessive allele on the unaffected (non-CNV) chromosome. Other considerations when determining pathogenicity include CNV dosage, X linkage, number of reports in the literature of an association between CNV and phenotype, and findings in “normal” individuals.

The American College of Medical Genetics has published guidelines for evaluating, interpreting, and reporting pathogenicity reflecting these principles. The recommended categories of clinical significance for reporting are pathogenic, uncertain clinical significance (likely pathogenic, likely benign, or no subclassification), or benign. The International Standards for Cytogenomic Arrays Consortium more recently proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support the interpretation of clinically significant copy number variation.” The proposal defined levels of evidence describe how well or how poorly detected variants or CNVs correlate with phenotype.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Lab tests for CMA testing and next-generation sequencing are available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

In 2010, the FDA indicated that it would require microarray manufacturers to seek clearance to sell their products for use in clinical cytogenetics.

CMA Testing

CMA testing is commercially available through many laboratories and includes targeted and whole-genome arrays, with or without SNV microarray analysis.

In January 2014, the Affymetrix CytoScan[®] Dx Assay (Thermo Fisher Scientific) was cleared by the FDA through the de novo 510(k) process. The FDA's review of the CytoScan Dx Assay included an analytic evaluation of the test's ability to detect accurately numerous chromosomal variations of different types, sizes, and genome locations compared with several analytically validated test methods. The FDA found that the CytoScan Dx Assay could detect CNVs across the genome and adequately detect CNVs in regions of the genome associated with developmental delay/intellectual disability. Reproducibility decreased with the CNV gain or loss size, particularly when less than approximately 400 kilobases (generally recommended as the lower reporting limit). As of July 2017, Affymetrix[™] has reported contains 2.7 million markers for copy number, 750,000 SNVs, and 1.9 million non-polymorphic probes (Affymetrix[™] was acquired by Thermo Fisher Scientific in 2016). FDA product code: PFX.

FirstStep^{Dx} PLUS[®] (Lineagen) uses Lineagen's custom-designed microarray platform manufactured by Affymetrix. As of July 2017, this microarray consists of a 2.8 million probe microarray for the detection of CNVs associated with neurodevelopmental disorders. The array includes probes that come standard on the Affymetrix CytoScan HD[®] microarray, with an additional 88435 custom probes designed by Lineagen.

Ambry Genetics offers multiple tests (CMA and next-generation sequencing) designed for diagnosing ASD and neurodevelopmental disorders. As of July 2017, the CMA offered by Ambry Genetics includes over 2.6 million probes for copy number and 750,000 SNV probes. The expanded next-generation sequencing panel for neurodevelopmental disorders assesses 196 genes.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

LabCorp offers the Reveal[®]‡ SNP Microarray-Pediatric for individuals with nonsyndromic congenital anomalies, dysmorphic features, developmental delay/intellectual disability, and/or ASD. The Reveal[®]‡ microarray has 2695 million probes as of July 2017.

Next-Generation Sequencing

A variety of commercial and academic laboratories offer next-generation sequencing panels designed for the evaluation of ASD, developmental delay/intellectual disability, and congenital anomalies, which vary in terms of the numbers of and specific genes tested.

Emory Genetics Laboratory offers an next-generation sequencing ASD panel of genes targeting genetic syndromes that include autism or autistic features. Greenwood Genetics Center offers an next-generation sequencing panel for syndromic autism that includes 83 genes. Fulgent Genetics offers an next-generation sequencing ASD panel that includes 121 genes.

Rationale/Source

Chromosomal microarray testing has been proposed for detection of genetic imbalances in infants or children with characteristics of developmental delay/intellectual disability, autism spectrum disorder, and/or congenital anomalies. CMA testing increases the diagnostic yield over karyotyping in children with the aforementioned characteristics, and CMA testing may impact clinical management decisions. Next-generation sequencing panel testing allows for the simultaneous analysis of a large number of genes and, in patients with normal CMA testing, the next-generation testing has been proposed as a way to identify single-gene causes of syndromes that have autism as a significant clinical feature.

For individuals who have developmental delay/intellectual disability, autism spectrum disorder, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive CMA testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision making, morbid events, and resource utilization. The available evidence supports test validity. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well-demonstrated. Direct evidence of improved outcomes with CMA compared with karyotyping is also lacking. However, for at least a subset of the disorders potentially diagnosed with CMA testing in this patient

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

population, there are well-defined and accepted management steps associated with positive test results. Further, there is evidence of changes in reproductive decision making as a result of positive test results. The information derived from CMA testing can accomplish the following: it could end a long diagnostic odyssey, or reduce morbidity for certain conditions by initiating surveillance/management of associated comorbidities, or it could impact future reproductive decision making for parents. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have developmental delay/intellectual disability, autism spectrum disorder, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive next-generation sequencing panel testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision making, morbid events, and resource utilization. The diagnostic yield associated with next-generation sequencing panel testing in this patient population is not well-characterized. The testing yield and likelihood of an uncertain result are variable, based on the gene panel, gene tested, and patient population; additionally, there are risks of uninterpretable and incidental results. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics issued a clinical report on the optimal medical genetics evaluation of a child with developmental delays or intellectual disability. Regarding CMA testing, this report stated

“CMA now should be considered a first-tier diagnostic test in all children with [global developmental delay/intellectual disability] GDD/ID for whom the causal diagnosis is not known... CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies.”

American Academy of Child and Adolescent Psychiatry

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

In 2014, the American Academy of Child and Adolescent Psychiatry updated its guidelines on the assessment and treatment of children and adolescents with ASD. The Academy recommended that “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.”

American Academy of Neurology and Child Neurology Society

In 2011, the American Academy of Neurology and the Child Neurology Society updated their guidelines on the evaluation of unexplained developmental delay and intellectual disability with information on genetic and metabolic (biochemical) testing to accommodate advances in the field. The guidelines concluded that CMA testing has the highest diagnostic yield in children with developmental delay/intellectual disability, that the “often complex results require confirmation and careful interpretation, often with the assistance of a medical geneticist,” and that CMA should be considered the “first-line” test. The guidelines acknowledged that “Research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis.”

American College of Medical Genetics

The American College of Medical Genetics (ACMG) (2010; reaffirmed 2020) published a clinical practice resource on array-based technologies and their clinical utilization for detecting chromosomal abnormalities. CMA testing for copy number variants was recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

- Multiple anomalies not specific to a well-delineated genetic syndrome
- Apparently nonsyndromic developmental delay/intellectual disability
- ASD.

Other ACMG guidelines have addressed the design and performance expectations for clinical microarrays and associated software and for the interpretation and reporting of copy number variants, both intended for the postnatal setting. A 2013 update included recommendations on the validation of microarray methodologies for both prenatal and postnatal specimens.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

The guideline revisions from ACMG (2013) stated that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of ASD is recommended, with the first tier including fragile X syndrome and CMA, and the second tier *MECP2* and *PTEN* testing. The guidelines stated that:

“this approach will evolve with continued advancements in diagnostic testing and improved understanding of the ASD phenotype. Multiple additional conditions have been reported in association with an ASD phenotype, but none of these has been evaluated in a large prospective cohort. Therefore, a future third tier of evaluation is a distinct possibility. Further studies would be needed to elevate the evidence to the point of recommended testing. Alternatively, advances in technology may permit bundling of individual tests into an extended, more readily accessible, and less expensive platform. The accumulating evidence using next-generation sequencing (third-tier testing) will increase the diagnostic yield even more over the next few years.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of [ClinicalTrials.gov](https://clinicaltrials.gov) in August 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies”, Policy 2.04.59, 06/2021.
2. Mikhail FM, Lose EJ, Robin NH, et al. Clinically relevant single gene or intragenic deletions encompassing critical neurodevelopmental genes in patients with developmental delay, mental retardation, and/or autism spectrum disorders. *Am J Med Genet A*. Oct 2011; 155A(10): 2386-96. PMID 22031302

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

3. Brandler WM, Sebat J. From de novo mutations to personalized therapeutic interventions in autism. *Annu Rev Med.* 2015; 66: 487-507. PMID 25587659
4. Stankiewicz P, Beaudet AL. Use of array CGH in the evaluation of dysmorphology, malformations, developmental delay, and idiopathic mental retardation. *Curr Opin Genet Dev.* Jun 2007; 17(3): 182-92. PMID 17467974
5. Stuart SW, King CH, Pai GS. Autism spectrum disorder, Klinefelter syndrome, and chromosome 3p21.31 duplication: a case report. *MedGenMed.* Dec 18 2007; 9(4): 60. PMID 18311409
6. Moeschler JB. Medical genetics diagnostic evaluation of the child with global developmental delay or intellectual disability. *Curr Opin Neurol.* Apr 2008; 21(2): 117-22. PMID 18317267
7. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders. *Genet Med.* Apr 2008; 10(4): 301-5. PMID 18414214
8. Korf BR, Rehm HL. New approaches to molecular diagnosis. *JAMA.* Apr 10 2013; 309(14): 1511-21. PMID 23571590
9. Kearney HM, South ST, Wolff DJ, et al. American College of Medical Genetics recommendations for the design and performance expectations for clinical genomic copy number microarrays intended for use in the postnatal setting for detection of constitutional abnormalities. *Genet Med.* Jul 2011; 13(7): 676-9. PMID 21681105
10. Rodriguez-Revenga L, Vallespin E, Madrigal I, et al. A parallel study of different array-CGH platforms in a set of Spanish patients with developmental delay and intellectual disability. *Gene.* May 25 2013; 521(1): 82-6. PMID 23524024
11. Kloosterman WP, Hochstenbach R. Deciphering the pathogenic consequences of chromosomal aberrations in human genetic disease. *Mol Cytogenet.* 2014; 7(1): 100. PMID 25606056
12. Kearney HM, Thorland EC, Brown KK, et al. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genet Med.* Jul 2011; 13(7): 680-5. PMID 21681106
13. Riggs ER, Church DM, Hanson K, et al. Towards an evidence-based process for the clinical interpretation of copy number variation. *Clin Genet.* May 2012; 81(5): 403-12. PMID 22097934
14. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). TEC Special Report: Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Developmental Delay/Mental Retardation and Autism Spectrum Disorder. TEC Assessments. 2009; Volume 24; Tab 10.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

15. Blue Cross and Blue Shield Association. Special Report: Chromosomal Microarray for the Genetic Evaluation of Patients With Global Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder. TEC Assessments. 2015; Volume 30; Tab 2.
16. Moeschler JB, Shevell M, Moeschler JB, et al. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*. Sep 2014; 134(3): e903-18. PMID 25157020
17. Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. *Neurology*. Feb 11 2003; 60(3): 367-80. PMID 12578916
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*. Washington (DC): American Psychiatric Association; 2013.
19. Zablotsky B, Black LI, Maenner MJ, et al. Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. *Pediatrics*. Oct 2019; 144(4). PMID 31558576
20. Srour M, Shevell M. Genetics and the investigation of developmental delay/intellectual disability. *Arch Dis Child*. Apr 2014; 99(4): 386-9. PMID 24344174
21. Willemsen MH, Kleefstra T. Making headway with genetic diagnostics of intellectual disabilities. *Clin Genet*. Feb 2014; 85(2): 101-10. PMID 23895455
22. Moeschler JB. Genetic evaluation of intellectual disabilities. *Semin Pediatr Neurol*. Mar 2008; 15(1): 2-9. PMID 18342255
23. Yuen RK, Thiruvahindrapuram B, Merico D, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. *Nat Med*. Feb 2015; 21(2): 185-91. PMID 25621899
24. Gaugler T, Klei L, Sanders SJ, et al. Most genetic risk for autism resides with common variation. *Nat Genet*. Aug 2014; 46(8): 881-5. PMID 25038753
25. Schaefer GB, Mendelsohn NJ. Genetics evaluation for the etiologic diagnosis of autism spectrum disorders. *Genet Med*. Jan 2008; 10(1): 4-12. PMID 18197051
26. Butler MG, Dasouki MJ, Zhou XP, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet*. Apr 2005; 42(4): 318-21. PMID 15805158
27. Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. *Lancet*. Apr 04 2015; 385(9975): 1305-14. PMID 25529582

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

28. Eriksson MA, Lieden A, Westerlund J, et al. Rare copy number variants are common in young children with autism spectrum disorder. *Acta Paediatr.* Jun 2015; 104(6): 610-8. PMID 25661985
29. Krepischi-Santos AC, Vianna-Morgante AM, Jehee FS, et al. Whole-genome array-CGH screening in undiagnosed syndromic patients: old syndromes revisited and new alterations. *Cytogenet Genome Res.* 2006; 115(3-4): 254-61. PMID 17124408
30. Bartnik M, Nowakowska B, Derwinska K, et al. Application of array comparative genomic hybridization in 256 patients with developmental delay or intellectual disability. *J Appl Genet.* Feb 2014; 55(1): 125-44. PMID 24297458
31. Bartnik M, Wisniowiecka-Kowalnik B, Nowakowska B, et al. The usefulness of array comparative genomic hybridization in clinical diagnostics of intellectual disability in children. *Dev Period Med.* Jul-Sep 2014; 18(3): 307-17. PMID 25182394
32. Chong WW, Lo IF, Lam ST, et al. Performance of chromosomal microarray for patients with intellectual disabilities/developmental delay, autism, and multiple congenital anomalies in a Chinese cohort. *Mol Cytogenet.* 2014; 7: 34. PMID 24926319
33. D'Amours G, Langlois M, Mathonnet G, et al. SNP arrays: comparing diagnostic yields for four platforms in children with developmental delay. *BMC Med Genomics.* Dec 24 2014; 7: 70. PMID 25539807
34. Henderson LB, Applegate CD, Wohler E, et al. The impact of chromosomal microarray on clinical management: a retrospective analysis. *Genet Med.* Sep 2014; 16(9): 657-64. PMID 24625444
35. Nava C, Keren B, Mignot C, et al. Prospective diagnostic analysis of copy number variants using SNP microarrays in individuals with autism spectrum disorders. *Eur J Hum Genet.* Jan 2014; 22(1): 71-8. PMID 23632794
36. Nicholl J, Waters W, Mulley JC, et al. Cognitive deficit and autism spectrum disorders: prospective diagnosis by array CGH. *Pathology.* Jan 2014; 46(1): 41-5. PMID 24300712
37. Palmer E, Speirs H, Taylor PJ, et al. Changing interpretation of chromosomal microarray over time in a community cohort with intellectual disability. *Am J Med Genet A.* Feb 2014; 164A(2): 377-85. PMID 24311194
38. Preiksaitiene E, Molyte A, Kasnauskiene J, et al. Considering specific clinical features as evidence of pathogenic copy number variants. *J Appl Genet.* May 2014; 55(2): 189-96. PMID 24535828

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

39. Redin C, Gerard B, Lauer J, et al. Efficient strategy for the molecular diagnosis of intellectual disability using targeted high-throughput sequencing. *J Med Genet.* Nov 2014; 51(11): 724-36. PMID 25167861
40. Roberts JL, Hovanes K, Dasouki M, et al. Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders or learning disability presenting for genetic services. *Gene.* Feb 01 2014; 535(1): 70-8. PMID 24188901
41. Stobbe G, Liu Y, Wu R, et al. Diagnostic yield of array comparative genomic hybridization in adults with autism spectrum disorders. *Genet Med.* Jan 2014; 16(1): 70-7. PMID 23765050
42. Tao VQ, Chan KY, Chu YW, et al. The clinical impact of chromosomal microarray on paediatric care in Hong Kong. *PLoS One.* 2014; 9(10): e109629. PMID 25333781
43. Utine GE, Haliloglu G, Volkan-Salanci B, et al. Etiological yield of SNP microarrays in idiopathic intellectual disability. *Eur J Paediatr Neurol.* May 2014; 18(3): 327-37. PMID 24508361
44. Uwineza A, Caberg JH, Hitayezu J, et al. Array-CGH analysis in Rwandan patients presenting development delay/intellectual disability with multiple congenital anomalies. *BMC Med Genet.* Jul 12 2014; 15: 79. PMID 25016475
45. Battaglia A, Doccini V, Bernardini L, et al. Confirmation of chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability, autism spectrum disorders and dysmorphic features. *Eur J Paediatr Neurol.* Nov 2013; 17(6): 589-99. PMID 23711909
46. Lee CG, Park SJ, Yun JN, et al. Array-based comparative genomic hybridization in 190 Korean patients with developmental delay and/or intellectual disability: a single tertiary care university center study. *Yonsei Med J.* Nov 2013; 54(6): 1463-70. PMID 24142652
47. Shoukier M, Klein N, Auber B, et al. Array CGH in patients with developmental delay or intellectual disability: are there phenotypic clues to pathogenic copy number variants?. *Clin Genet.* Jan 2013; 83(1): 53-65. PMID 22283495
48. Sorte HS, Gjevik E, Sponheim E, et al. Copy number variation findings among 50 children and adolescents with autism spectrum disorder. *Psychiatr Genet.* Apr 2013; 23(2): 61-9. PMID 23277134
49. Filges I, Suda L, Weber P, et al. High resolution array in the clinical approach to chromosomal phenotypes. *Gene.* Mar 10 2012; 495(2): 163-9. PMID 22240311

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

50. Iourov IY, Vorsanova SG, Kurinnaia OS, et al. Molecular karyotyping by array CGH in a Russian cohort of children with intellectual disability, autism, epilepsy and congenital anomalies. *Mol Cytogenet.* Dec 31 2012; 5(1): 46. PMID 23272938
51. McGrew SG, Peters BR, Crittendon JA, et al. Diagnostic yield of chromosomal microarray analysis in an autism primary care practice: which guidelines to implement?. *J Autism Dev Disord.* Aug 2012; 42(8): 1582-91. PMID 22089167
52. Tzetis M, Kitsiou-Tzeli S, Frysira H, et al. The clinical utility of molecular karyotyping using high-resolution array-comparative genomic hybridization. *Expert Rev Mol Diagn.* Jun 2012; 12(5): 449-57. PMID 22702362
53. Bremer A, Giacobini M, Eriksson M, et al. Copy number variation characteristics in subpopulations of patients with autism spectrum disorders. *Am J Med Genet B Neuropsychiatr Genet.* Mar 2011; 156(2): 115-24. PMID 21302340
54. Coulter ME, Miller DT, Harris DJ, et al. Chromosomal microarray testing influences medical management. *Genet Med.* Sep 2011; 13(9): 770-6. PMID 21716121
55. Wincent J, Anderlid BM, Lagerberg M, et al. High-resolution molecular karyotyping in patients with developmental delay and/or multiple congenital anomalies in a clinical setting. *Clin Genet.* Feb 2011; 79(2): 147-57. PMID 20486943
56. Manolakos E, Vetro A, Kefalas K, et al. The use of array-CGH in a cohort of Greek children with developmental delay. *Mol Cytogenet.* Nov 09 2010; 3: 22. PMID 21062444
57. Rosenfeld JA, Ballif BC, Torchia BS, et al. Copy number variations associated with autism spectrum disorders contribute to a spectrum of neurodevelopmental disorders. *Genet Med.* Nov 2010; 12(11): 694-702. PMID 20808228
58. Schaefer GB, Starr L, Pickering D, et al. Array comparative genomic hybridization findings in a cohort referred for an autism evaluation. *J Child Neurol.* Dec 2010; 25(12): 1498-503. PMID 20729506
59. Shen Y, Dies KA, Holm IA, et al. Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics.* Apr 2010; 125(4): e727-35. PMID 20231187
60. Bruno DL, Ganesamoorthy D, Schoumans J, et al. Detection of cryptic pathogenic copy number variations and constitutional loss of heterozygosity using high resolution SNP microarray analysis in 117 patients referred for cytogenetic analysis and impact on clinical practice. *J Med Genet.* Feb 2009; 46(2): 123-31. PMID 19015223

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

61. Friedman J, Adam S, Arbour L, et al. Detection of pathogenic copy number variants in children with idiopathic intellectual disability using 500 K SNP array genomic hybridization. *BMC Genomics*. Nov 16 2009; 10: 526. PMID 19917086
62. Baldwin EL, Lee JY, Blake DM, et al. Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. *Genet Med*. Jun 2008; 10(6): 415-29. PMID 18496225
63. Christian SL, Brune CW, Sudi J, et al. Novel submicroscopic chromosomal abnormalities detected in autism spectrum disorder. *Biol Psychiatry*. Jun 15 2008; 63(12): 1111-7. PMID 18374305
64. Marshall CR, Noor A, Vincent JB, et al. Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet*. Feb 2008; 82(2): 477-88. PMID 18252227
65. Pickering DL, Eudy JD, Olney AH, et al. Array-based comparative genomic hybridization analysis of 1176 consecutive clinical genetics investigations. *Genet Med*. Apr 2008; 10(4): 262-6. PMID 18414209
66. Saam J, Gudgeon J, Aston E, et al. How physicians use array comparative genomic hybridization results to guide patient management in children with developmental delay. *Genet Med*. Mar 2008; 10(3): 181-6. PMID 18344707
67. Shevell MI, Bejjani BA, Srour M, et al. Array comparative genomic hybridization in global developmental delay. *Am J Med Genet B Neuropsychiatr Genet*. Oct 05 2008; 147B(7): 1101-8. PMID 18361433
68. Aradhya S, Manning MA, Splendore A, et al. Whole-genome array-CGH identifies novel contiguous gene deletions and duplications associated with developmental delay, mental retardation, and dysmorphic features. *Am J Med Genet A*. Jul 01 2007; 143A(13): 1431-41. PMID 17568414
69. Ballif BC, Sulpizio SG, Lloyd RM, et al. The clinical utility of enhanced subtelomeric coverage in array CGH. *Am J Med Genet A*. Aug 15 2007; 143A(16): 1850-7. PMID 17632771
70. Froyen G, Van Esch H, Bauters M, et al. Detection of genomic copy number changes in patients with idiopathic mental retardation by high-resolution X-array-CGH: important role for increased gene dosage of XLMR genes. *Hum Mutat*. Oct 2007; 28(10): 1034-42. PMID 17546640
71. Hoyer J, Dreweke A, Becker C, et al. Molecular karyotyping in patients with mental retardation using 100K single-nucleotide polymorphism arrays. *J Med Genet*. Oct 2007; 44(10): 629-36. PMID 17601928

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

72. Lu X, Shaw CA, Patel A, et al. Clinical implementation of chromosomal microarray analysis: summary of 2513 postnatal cases. *PLoS One*. Mar 28 2007; 2(3): e327. PMID 17389918
73. Madrigal I, Rodriguez-Revena L, Armengol L, et al. X-chromosome tiling path array detection of copy number variants in patients with chromosome X-linked mental retardation. *BMC Genomics*. Nov 29 2007; 8: 443. PMID 18047645
74. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. *Science*. Apr 20 2007; 316(5823): 445-9. PMID 17363630
75. Shen Y, Irons M, Miller DT, et al. Development of a focused oligonucleotide-array comparative genomic hybridization chip for clinical diagnosis of genomic imbalance. *Clin Chem*. Dec 2007; 53(12): 2051-9. PMID 17901113
76. Thuresson AC, Bondeson ML, Edeby C, et al. Whole-genome array-CGH for detection of submicroscopic chromosomal imbalances in children with mental retardation. *Cytogenet Genome Res*. 2007; 118(1): 1-7. PMID 17901693
77. Wagenstaller J, Spranger S, Lorenz-Depiereux B, et al. Copy-number variations measured by single-nucleotide-polymorphism oligonucleotide arrays in patients with mental retardation. *Am J Hum Genet*. Oct 2007; 81(4): 768-79. PMID 17847001
78. Ballif BC, Rorem EA, Sundin K, et al. Detection of low-level mosaicism by array CGH in routine diagnostic specimens. *Am J Med Genet A*. Dec 15 2006; 140(24): 2757-67. PMID 17103431
79. Friedman JM, Baross A, Delaney AD, et al. Oligonucleotide microarray analysis of genomic imbalance in children with mental retardation. *Am J Hum Genet*. Sep 2006; 79(3): 500-13. PMID 16909388
80. Jacquemont ML, Sanlaville D, Redon R, et al. Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. *J Med Genet*. Nov 2006; 43(11): 843-9. PMID 16840569
81. Lugtenberg D, de Brouwer AP, Kleefstra T, et al. Chromosomal copy number changes in patients with non-syndromic X linked mental retardation detected by array CGH. *J Med Genet*. Apr 2006; 43(4): 362-70. PMID 16169931
82. Menten B, Maas N, Thienpont B, et al. Emerging patterns of cryptic chromosomal imbalance in patients with idiopathic mental retardation and multiple congenital anomalies: a new series of 140 patients and review of published reports. *J Med Genet*. Aug 2006; 43(8): 625-33. PMID 16490798

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

83. Miyake N, Shimokawa O, Harada N, et al. BAC array CGH reveals genomic aberrations in idiopathic mental retardation. *Am J Med Genet A*. Feb 01 2006; 140(3): 205-11. PMID 16419101
84. Rosenberg C, Knijnenburg J, Bakker E, et al. Array-CGH detection of micro rearrangements in mentally retarded individuals: clinical significance of imbalances present both in affected children and normal parents. *J Med Genet*. Feb 2006; 43(2): 180-6. PMID 15980116
85. Shaffer LG, Kashork CD, Saleki R, et al. Targeted genomic microarray analysis for identification of chromosome abnormalities in 1500 consecutive clinical cases. *J Pediatr*. Jul 2006; 149(1): 98-102. PMID 16860135
86. Sharp AJ, Hansen S, Selzer RR, et al. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. *Nat Genet*. Sep 2006; 38(9): 1038-42. PMID 16906162
87. de Vries BB, Pfundt R, Leisink M, et al. Diagnostic genome profiling in mental retardation. *Am J Hum Genet*. Oct 2005; 77(4): 606-16. PMID 16175506
88. Schoumans J, Ruivenkamp C, Holmberg E, et al. Detection of chromosomal imbalances in children with idiopathic mental retardation by array based comparative genomic hybridisation (array-CGH). *J Med Genet*. Sep 2005; 42(9): 699-705. PMID 16141005
89. Tyson C, Harvard C, Locker R, et al. Submicroscopic deletions and duplications in individuals with intellectual disability detected by array-CGH. *Am J Med Genet A*. Dec 15 2005; 139(3): 173-85. PMID 16283669
90. Harada N, Hatchwell E, Okamoto N, et al. Subtelomere specific microarray based comparative genomic hybridisation: a rapid detection system for cryptic rearrangements in idiopathic mental retardation. *J Med Genet*. Feb 2004; 41(2): 130-6. PMID 14757861
91. Shaw-Smith C, Redon R, Rickman L, et al. Microarray based comparative genomic hybridisation (array-CGH) detects submicroscopic chromosomal deletions and duplications in patients with learning disability/mental retardation and dysmorphic features. *J Med Genet*. Apr 2004; 41(4): 241-8. PMID 15060094
92. Vissers LE, de Vries BB, Osoegawa K, et al. Array-based comparative genomic hybridization for the genomewide detection of submicroscopic chromosomal abnormalities. *Am J Hum Genet*. Dec 2003; 73(6): 1261-70. PMID 14628292
93. Chaves TF, Baretto N, Oliveira LF, et al. Copy Number Variations in a Cohort of 420 Individuals with Neurodevelopmental Disorders From the South of Brazil. *Sci Rep*. Nov 28 2019; 9(1): 17776. PMID 31780800

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

94. Hu T, Zhang Z, Wang J, et al. Chromosomal Aberrations in Pediatric Patients with Developmental Delay/Intellectual Disability: A Single-Center Clinical Investigation. *Biomed Res Int.* 2019; 2019: 9352581. PMID 31781653
95. Xu M, Ji Y, Zhang T, et al. Clinical Application of Chromosome Microarray Analysis in Han Chinese Children with Neurodevelopmental Disorders. *Neurosci Bull.* Dec 2018; 34(6): 981-991. PMID 29948840
96. Sansovic I, Ivankov AM, Bobinec A, et al. Chromosomal microarray in clinical diagnosis: a study of 337 patients with congenital anomalies and developmental delays or intellectual disability. *Croat Med J.* Jun 14 2017; 58(3): 231-238. PMID 28613040
97. Ho KS, Twede H, Vanzo R, et al. Clinical Performance of an Ultrahigh Resolution Chromosomal Microarray Optimized for Neurodevelopmental Disorders. *Biomed Res Int.* 2016; 2016: 3284534. PMID 27975050
98. Ho KS, Wassman ER, Baxter AL, et al. Chromosomal Microarray Analysis of Consecutive Individuals with Autism Spectrum Disorders Using an Ultra-High Resolution Chromosomal Microarray Optimized for Neurodevelopmental Disorders. *Int J Mol Sci.* Dec 09 2016; 17(12). PMID 27941670
99. Hu G, Fan Y, Wang L, et al. Copy number variations in 119 Chinese children with idiopathic short stature identified by the custom genome-wide microarray. *Mol Cytogenet.* 2016; 9: 16. PMID 26884814
100. Lu XY, Phung MT, Shaw CA, et al. Genomic imbalances in neonates with birth defects: high detection rates by using chromosomal microarray analysis. *Pediatrics.* Dec 2008; 122(6): 1310-8. PMID 19047251
101. Gogarty B. Parents as partners. A report and guidelines on the investigation of children with developmental delay; by parents, for professionals Cambridge: Cambridge Genetics Knowledge Park; 2006.
102. Mroch AR, Flanagan JD, Stein QP. Solving the puzzle: case examples of array comparative genomic hybridization as a tool to end the diagnostic odyssey. *Curr Probl Pediatr Adolesc Health Care.* Mar 2012; 42(3): 74-8. PMID 22325475
103. Turner G, Boyle J, Partington MW, et al. Restoring reproductive confidence in families with X-linked mental retardation by finding the causal mutation. *Clin Genet.* Feb 2008; 73(2): 188-90. PMID 18070138
104. Linggen M, Albers L, Borchers M, et al. Obtaining a genetic diagnosis in a child with disability: impact on parental quality of life. *Clin Genet.* Feb 2016; 89(2): 258-66. PMID 26084449

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

105. Hayeems RZ, Hoang N, Chenier S, et al. Capturing the clinical utility of genomic testing: medical recommendations following pediatric microarray. *Eur J Hum Genet.* Sep 2015; 23(9): 1135-41. PMID 25491637
106. Ellison JW, Ravnan JB, Rosenfeld JA, et al. Clinical utility of chromosomal microarray analysis. *Pediatrics.* Nov 2012; 130(5): e1085-95. PMID 23071206
107. Hoffmann TJ, Windham GC, Anderson M, et al. Evidence of reproductive stoppage in families with autism spectrum disorder: a large, population-based cohort study. *JAMA Psychiatry.* Aug 2014; 71(8): 943-51. PMID 24942798
108. Grozeva D, Carss K, Spasic-Boskovic O, et al. Targeted Next-Generation Sequencing Analysis of 1,000 Individuals with Intellectual Disability. *Hum Mutat.* Dec 2015; 36(12): 1197-204. PMID 26350204
109. Kalsner L, Twachtman-Bassett J, Tokarski K, et al. Genetic testing including targeted gene panel in a diverse clinical population of children with autism spectrum disorder: Findings and implications. *Mol Genet Genomic Med.* Mar 2018; 6(2): 171-185. PMID 29271092
110. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry.* Feb 2014; 53(2): 237-57. PMID 24472258
111. Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* Oct 25 2011; 77(17): 1629-35. PMID 21956720
112. Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* Nov 2010; 12(11): 742-5. PMID 20962661
113. Manning M, Hudgins L. Addendum: Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* Jun 08 2020. PMID 32514088
114. South ST, Lee C, Lamb AN, et al. ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. *Genet Med.* Nov 2013; 15(11): 901-9. PMID 24071793
115. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* May 2013; 15(5): 399-407. PMID 23519317

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

Policy History

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

- 11/03/2016 Medical Policy Committee review
 - 11/16/2016 Medical Policy Implementation Committee approval. New policy.
 - 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
 - 11/02/2017 Medical Policy Committee review
 - 11/15/2017 Medical Policy Implementation Committee approval. The first policy statement was revised to remove the “postnatal” term; a second statement was added that chromosomal microarray analysis is investigational for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay.
 - 11/08/2018 Medical Policy Committee review
 - 11/21/2018 Medical Policy Implementation Committee approval. No change to coverage.
 - 11/07/2019 Medical Policy Committee review
 - 11/13/2019 Medical Policy Implementation Committee approval. No change to coverage.
 - 11/05/2020 Medical Policy Committee review
 - 11/11/2020 Medical Policy Implementation Committee approval. No change to coverage.
 - 11/04/2021 Medical Policy Committee review
 - 11/10/2021 Medical Policy Implementation Committee approval. No change to coverage.
 - 12/20/2021 Coding Update
 - 02/04/2022 Coding Update
 - 03/20/2022 Coding Update
- Next Scheduled Review Date: 11/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0209U, 81228, 81229, 81479 Add code effective 1/1/2022: 81349 Delete code effective 4/1/2022: 0156U, 0170U, 0260U, 0263U, 81470, 81471 Add code effective 4/1/2022: 0318U
HCPCS	S3870
ICD-10 Diagnosis	F70-F79, F80.0-F80.9, F81.0-F81.9, F82, F84.0, F88, F89, H93.25, R48.0 Add DX code eff 10/1/21: F78.A1, F78.A9

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Policy # 00536

Original Effective Date: 11/16/2016

Current Effective Date: 12/13/2021

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2022 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.