GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND CONGENITAL ANOMALIES

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND CONGENITAL ANOMALIES (cont.)

Description:

Chromosomal microarray testing (CMA) is a laboratory test that increases the chromosomal resolution for detection of abnormalities. The term CMA collectively describes two different platforms: array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays. Both types of arrays can identify loss or gain of DNA (microdeletions or microduplications) known as copy number variants (CNV).

CMA testing has been used for detection of genetic imbalances in infants or children with characteristics of autism spectrum disorder (ASD), developmental delay/intellectual disability (DD/ID) and congenital anomalies. It has also been investigated as a prenatal test of a fetus that may be at high risk for a chromosomal abnormality.

Developmental Delay (DD)/ Intellectual Disability (ID):
The diagnosis of DD is reserved for children younger than 5 years of age who have a significant delay in two or more of the following developmental domains: gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living. Intellectual disability (ID) is a lifelong disability diagnosed at or after 5 years of age when IQ testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), of the American Psychiatric Association defined individuals with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than 2 areas of adaptive behavior or systems of support.

Autism Spectrum Disorder (ASD):
According to DSM-IV, pervasive developmental disorders (PDD) encompass 5 conditions: autistic disorder, Asperger disorder, pervasive developmental disorder–not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Rett syndrome. Although not mentioned in the DSM-IV, autism spectrum disorder (ASD) includes the first three on the list.

One of the major changes between DSM-IV and DSM-5 is the new diagnostic criteria for ASD, which include removing the term pervasive developmental disorders. Researchers found that the separate diagnoses included in PDD were not consistently applied across different clinics and treatment centers. Under DSM-5, ASD now encompasses the previous DSM-IV autistic disorder (autism), Asperger disorder, childhood disintegrative disorder, and PDD-NOS. Anyone diagnosed with one of the PDDs from DSM-IV should still meet the criteria for ASD in DSM-5.
GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND CONGENITAL ANOMALIES (cont.)

Description: (cont.)

Congenital Anomalies:
In the United States, congenital anomalies are the leading cause of neonatal morbidity and mortality. Genetic factors have been identified as an important cause for congenital anomalies. Common chromosomal aneuploidies (e.g., monosomy X, trisomies 21, 18, and 13) have traditionally been diagnosed in the neonatal period using conventional karyotyping. Improved methods, such as fluorescence in situ hybridization (FISH) using chromosome or locus-specific probes, enable the diagnosis of some of the common microdeletion syndromes (e.g., DiGeorge and velocardiofacial syndromes, cri-du-chat syndrome, Prader-Willi and Angelman syndromes). However, FISH is applicable only in individuals with a strong clinical suspicion of a specific genetic defect, which may be difficult to detect in a neonate with congenital anomalies, because clinical presentation may be atypical or have nonspecific phenotypic features that may be shared by several different disorders, or a young individual may lack specific syndromic features that appear at a later age. An improved rate of detection of copy number variants (CNVs) has been shown with the use of array comparative genomic hybridization (aCGH).

Tests include, but are not limited to:

- Affymetrix CytoScan® Dx Assay
- FirstStepDx PLUS® (postnatal)
- GenomeDx whole genome array (postnatal)
- Reveal® SNP microarray-Pediatric
- SignatureChipOS® microarray (postnatal)

Next generation sequencing (NGS) panel testing allows for simultaneous analysis of multiple genes, and has been investigated as a way to identify single gene causes of syndromes that have autism as a significant clinical feature, in individuals with normal array-based testing.

Tests include, but are not limited to:

- devSEEK® and devSEEK Triome™
- devACT® Clinical Management Panel
- Mount Sinai School of Medicine Department of Genetics 30 Gene Sequencing Panel Autism
- X-Linked Intellectual Disability (XLID), Greenwood Genetic Center
- X-Linked Intellectual Disability Gene Panel, Emory Genetics Laboratory
GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND CONGENITAL ANOMALIES (cont.)

Definitions:

Genetic Testing:
Analysis of DNA, RNA, chromosomes, proteins and certain metabolites in order to detect alterations related to an inherited disorder.

Gene:
A hereditary unit consisting of segments of DNA that occupies a specific location on chromosomes. Genes undergo mutation when their DNA sequence changes.

Genetic Counseling:
Instruction that provides interpretation of genetic tests and information about courses of action that are available for the care of an individual with a genetic disorder or for future family planning.

Affected Individual:
An individual displaying signs or symptoms characteristic of a suspected or specific inherited disorder.

Unaffected Individual:
An individual who displays no signs or symptoms characteristic of a suspected or specific inherited disorder.

Screening:
Genetic screening is the testing of an individual with no symptoms for a specific inherited disorder to determine if the individual carries an abnormal gene. Screening can be used to predict risk or potential risk for the individual or their offspring.

Criteria:

Other BCBSAZ Medical Coverage Guidelines may exist for diagnoses not addressed in this guideline.

- Genetic testing and/or counseling of an unaffected individual, regardless of risk factors is considered screening and not eligible for coverage.

- Genetic testing and/or counseling of an affected individual to confirm a disease when confirmation of the diagnosis would not impact the care and/or management is considered not medically necessary and not eligible for coverage.
GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND CONGENITAL (cont.)

Criteria: (cont.)

- Chromosomal microarray analysis of an **affected** individual is considered **medically necessary** as first-line testing in the initial evaluation with documentation of ANY of the following:
  1. Apparently nonsyndromic developmental delay/intellectual disability
  2. Autism spectrum disorder
  3. Multiple congenital anomalies not specific to a well-delineated genetic syndrome

- Chromosomal microarray analysis for all other indications not previously listed or if above criteria not met is considered **experimental or investigational** based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

These indications include, **but are not limited to:**

- Idiopathic growth or language delay

- Genetic testing and/or counseling using panel testing with next generation sequencing in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability or autism spectrum disorder or congenital anomalies is considered **experimental or investigational** based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.
GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND CONGENITAL ANOMALIES (cont.)

Resources:

Literature reviewed 09/12/17. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 03/20/2013 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


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AUTISM SPECTRUM DISORDER AND CONGENITAL ANOMALIES (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah níliningíí Blue Cross Blue Shield of Arizona haada yít’éego bína’ídlíkidgo éí doocado Háida bií aniiyeedííí t’áadóó le’ éí yina’ídlíkidgo beehaz’ááníi hóółó dúú Díí t’áá hazaadd’éhí háká a’doooolgo bee ház’a doo báah níliningóó. Aта’ halne’íígíí kojí’ bíIchí’í’ hodóólnííh 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thống dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو أدى شخص تساعدك أسسه حالة بخصوص المواقع الضرورية بلغتك من دون أي تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.
GENETIC TESTING FOR DEVELOPMENTAL DELAY/INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND CONGENITAL ANOMALIES (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, ay mga may katarungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuhang tulong at impormasyon sa iyong wika ng walang gastos. Upang makaasap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 동역사와 얘기하기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi: اگر شما یا کسی که شما به آن کمک می‌کنید، سوال در مورد اطلاعات به زبان خود را به طور رایگان دریافت نمایید. 877-475-4799.

Assyrian: Blue Cross Blue Shield of Arizona، سی‌سی‌بی‌بی‌سی‌دی، شما، شما، شما، شما، شما، شما. 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณหรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสมควรจะได้รับความช่วยเหลือและข้อมูลภาษาของคุณได้โดยไม่ค่าใช้จ่าย โปรดโทรมา โทร 877-475-4799.