GENETIC TESTING FOR FMR1 VARIANTS INCLUDING FRAGILE X SYNDROME

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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(cont.)

Description:
Fragile X syndrome (FXS) is the most common inherited form of mental disability and known genetic cause of autism. In addition to the intellectual impairment, individuals may present with typical facial characteristics such as an elongated face with a prominent forehead, protruding jaw, and large ears. Connective tissue anomalies include hyperextensible finger and thumb joints, hand calluses, velvet-like skin, flat feet and mitral valve prolapse. The characteristic appearance of adult males includes macroorchidism. Individuals may exhibit behavioral problems including autism spectrum disorders, sleeping problems, social anxiety, poor eye contact, mood disorders and hand-flapping or biting. Another prominent feature of the disorder is neuronal hyperexcitability, manifested by hyperactivity, increased sensitivity to sensory stimuli and a high incidence of epileptic seizures.

FXS is associated with the expansion of the CGG trinucleotide repeat in the fragile X mental retardation 1 (FMR1) gene on the X chromosome. Diagnosis of FXS may include using a genetic test that determines the number of CGG repeats in the fragile X gene. The individual is classified as normal, intermediate (or “gray zone”), premutation or full mutation based on the number of CGG repeats.

Full mutation: >200-230 CGG repeats (methylated)
Premutation: 55-200 CGG repeats (unmethylated)
Intermediate: 45-54 CGG repeats (unmethylated)
Normal: 5-44 CGG repeats (unmethylated)

Individuals with FMR1 premutations are carriers and may have a FMR1-related disorder including fragile X-associated tremor/ataxia syndrome (FXTAS) or premature ovarian insufficiency (POI).

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.

Infertility:
Inability of a couple to conceive after one year of unprotected intercourse.
GENETIC TESTING FOR FMR1 VARIANTS INCLUDING FRAGILE X SYNDROME (cont.)

Definitions: (cont.)

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:

For genetic testing for developmental delay, intellectual disability, autism spectrum disorder and congenital anomalies, see BCBSAZ Medical Coverage Guideline #O706, “Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder and Congenital Anomalies”.

- 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 and/or counseling of an affected individual with intellectual disability, developmental delay or autism spectrum disorder for FMR1 variants is considered medically necessary.
- Genetic testing and/or counseling of an affected individual or their relatives with a positive cytogenetic fragile X test result who are seeking counseling related to the risk of carrier status among themselves or their relatives is considered medically necessary.
- Genetic testing and/or counseling of an affected woman with primary ovarian failure under the age of 40 in whom fragile x-associated ovarian failure is suspected is considered medically necessary.
- Genetic testing and/or counseling of an affected individual with neurologic symptoms consistent with fragile X-associated tremor/ataxia syndrome is considered medically necessary.
GENETIC TESTING FOR FMR1 VARIANTS INCLUDING FRAGILE X SYNDROME
(cont.)

Criteria: (cont.)

- Preconception or prenatal and/or infertility 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.

- Preconception, prenatal and/or infertility genetic testing and/or counseling of an unaffected individual for the FMR1 mutation regardless of risk factors is considered screening and not eligible for coverage.

Examples include, but are not limited to:

- Prenatal testing of fetus of known carrier mother
- Individual with family history of fragile X syndrome or of undiagnosed intellectual disability

Resources:

Literature reviewed 02/20/18. 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 10/15/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.

GENETIC TESTING FOR FMR1 VARIANTS INCLUDING FRAGILE X SYNDROME (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 nilinígíí Blue Cross Blue Shield of Arizona haata yit’éego bíná’ilíkidgo éí doodago Háída bii Naaniyeeeldígíí t’áadooo le’ é yina’ilíkidigo beehaaz’aanii hóó díí t’áa hazaadke’éhí hábak a’doo wóolgo bee haz’a doo báah’ilíniligoó. Ata’ halne’iligíi kojí bích’é’ hodínilíní 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插秧項目的名稱 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 thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو أدى شخص تساعد أو متابعة بخصوص موضوعة藍十字藍盾阿茲（Blue Cross Blue Shield of Arizona）نقرة على المساعدة والموارد الضرورية في ذلك من دون أي تكلفة. للتحدث مع متجر أتصل به 877-475-4799.
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(cont.)

Multi-Language Interpreter Services: (cont.)

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

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관한 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통해서 귀하에게는 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:

اهرا شما، یا کسی که شما به او کمک میکنید، سوال‌ها را مطرح نمایید. اطلاعات به زبان خود را به طور رایگان دریافت کنید. 877-475-4799.

Assyrian:

Blue Cross Blue Shield of Arizona ەیەکە لە سەمەنی سەکەکە لە شەوەیەکە بە ئەکەڵ بەکەیە تەوا ۆسەکەکە، ئەکەڵەکە، ئەکەڵەکە نەمەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە، ئەکەڵەکە.

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 prevodilcem, nazovite 877-475-4799.

Thai: หากคุณหรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสามารถจะได้รับความช่วยเหลือและข้อมูลในภาษาของคุณโดยไม่เสียเงิน พลังงานตาม โทร 877-475-4799.