GENETIC TESTING FOR MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS AND RELATED DISORDERS

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 MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS AND RELATED DISORDERS (cont.)

**Description:**

Marfan syndrome (MFS) is a systemic connective tissue disorder that may have a high degree of clinical variability and overlapping phenotypes with other syndromes and disorders. The diagnosis of most suspected connective tissue disorders can be made based on clinical findings and family history. Some of these disorders are associated with a predisposition to the development of progressive thoracic aortic aneurysms (TAAs) and dissection (TAAD). Accurate diagnosis of one of these syndromes can lead to changes in clinical management, including surveillance of the aorta and surgical repair of the aorta, when necessary.

Known pathogenic variants are associated with MFS and the other connective tissue disorders that may share clinical features with MFS. Therefore, genetic testing has been proposed as a means of diagnosis. Genetic testing has conventionally been used in situations in which a definitive diagnosis of one of these conditions cannot be made.

More recently, panels using next-generation sequencing (NGS), which test for multiple genes simultaneously, have been investigated for the syndromes that are associated with thoracic aortic aneurysms and dissections, and other conditions that may have overlapping phenotypes.

Syndromes or disorders associated with TAAD include:

<table>
<thead>
<tr>
<th>Syndrome or Disorder</th>
<th>Major Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan syndrome</td>
<td>• FBN1</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome (EDS) type IV</td>
<td>• COL3A1</td>
</tr>
<tr>
<td>(vascular type)</td>
<td></td>
</tr>
<tr>
<td>Loeys-Dietz Syndrome (LDS)</td>
<td>• TGFBR1</td>
</tr>
<tr>
<td></td>
<td>• TGFBR2</td>
</tr>
<tr>
<td></td>
<td>• SMAD3</td>
</tr>
<tr>
<td></td>
<td>• TGBF2</td>
</tr>
<tr>
<td>Familial TAAD</td>
<td>• TGFBR1</td>
</tr>
<tr>
<td></td>
<td>• TGFBR2</td>
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<tr>
<td></td>
<td>• MYH11</td>
</tr>
<tr>
<td></td>
<td>• ACTA2</td>
</tr>
<tr>
<td></td>
<td>• FBN1</td>
</tr>
<tr>
<td></td>
<td>• MYLK</td>
</tr>
<tr>
<td></td>
<td>• SMAD3</td>
</tr>
<tr>
<td>Arterial tortuosity syndrome</td>
<td>• SLC2A10</td>
</tr>
</tbody>
</table>
GENETIC TESTING FOR MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS AND RELATED DISORDERS (cont.)

Description: (cont.)

Syndromes or disorders not associated with TAAD include:

<table>
<thead>
<tr>
<th>Syndrome or Disorder</th>
<th>Major Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED12-related disorders (FS syndrome type 1 and Lujan syndrome)</td>
<td>▪ MED12</td>
</tr>
<tr>
<td>Shprintzen-Goldberg Syndrome</td>
<td>▪ SK1</td>
</tr>
<tr>
<td>EDS classic type (EDS I and II)</td>
<td>▪ COL5A1</td>
</tr>
<tr>
<td>EDS kyphoscoliotic form (EDS type VI)</td>
<td>▪ COL5A2</td>
</tr>
<tr>
<td>Periventricular heterotopia, EDS variant</td>
<td>▪ PLOD1</td>
</tr>
<tr>
<td>Congenital contractural Arachnodactyly</td>
<td>▪ FLNA</td>
</tr>
<tr>
<td></td>
<td>▪ FBN2</td>
</tr>
</tbody>
</table>

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.
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:

- 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 for individual genetic testing for the diagnosis of Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, is considered medically necessary with documentation of ALL of the following:
  1. Testing is limited to the following genes: FBN1 and MYH11 and ACTA2, TGFBR1, and TGFBR 2
  2. Signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made using established clinical diagnostic criteria

- Genetic testing and/or counseling for individual genetic testing for all Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders 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.
GENETIC TESTING FOR MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS AND RELATED DISORDERS (cont.)

Criteria: (cont.)

- Genetic testing panels and/or counseling for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders 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.

These panels include, but are not limited to:

- Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehlers-Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3 and MYLK
- Duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11 and COL3A1

Resources:

Literature reviewed 03/06/18. 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.

GENETIC TESTING FOR MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS AND RELATED DISORDERS (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 niliniígíí Blue Cross Blue Shield of Arizona haada ylt’éégo bíná’dílíkidgo éí doodago Háida bígí aniyeedííí t’áadoo le’é yina’dílíkidgo beeház’ áaníí hólo díí t’áá hazaad’ ehi háká a’dooowolgo bee haz’á doo baqáh ilínígóó. Atá’ halné’éíííí koj’ bích’í’ hodilííhíí 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 chuyển với một thợ dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعدته أسئلة بخصوص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.
GENETIC TESTING FOR MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS AND RELATED DISORDERS (cont.)

Multi-Language Interpreter Services: (cont.)

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

Korean: 안녕 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하의 도움과 정보를 귀하의 언어로 이용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통해서 귀하가 877-475-4799 로 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: آگاهی‌بانی که شما به آن یا کمک می‌کنید، سوال‌های مربوط به Blue Cross Blue Shield of Arizona را در هر زبان صحبت‌کننده‌ای به شما می‌تواند با برداشتن هزینه ارائه دهد. شما می‌توانید با 877-475-4799 تماس حاصل نمایید.

Assyrian: Blue Cross Blue Shield of Arizona دوسته، یا کمک که به آن یا کمک می‌کنید، سوال‌های مربوط به Blue Cross Blue Shield of Arizona را در هر زبان صحبت‌کننده‌ای به شما می‌تواند ارائه دهد. شما می‌توانید با 877-475-4799 تماس حاصل نمایید.

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: หากคุณหรือคนที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสามารถติดต่อสอบถามเจ้าหน้าที่เพื่อแจ้งข้อมูลทางโทรศัพท์หมายเลข 877-475-4799.