GENETIC TESTING FOR CARDIAC ION CHANNELOPATHIES

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 CARDIAC ION CHANNELOPATHIES (cont.)

Description:

Genetic testing is available for individuals suspected of having cardiac ion channelopathies, including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and short QT syndrome (SQTS). These disorders are clinically heterogeneous and may range from asymptomatic to presenting with sudden cardiac death (SCD).

Cardiac ion channelopathies are the result of mutations in genes that code for protein subunits of the cardiac ion channels. These channels are essential cell membrane components that open or close to allow ions to flow into or out of the cell and are essential for the maintenance of a normal cardiac action potential. This group of disorders is associated with ventricular arrhythmias and an increased risk of SCD.

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.

1st Degree Relative:
Blood-related sibling, parent or child.

2nd Degree Relative:
A relative removed by one generation, e.g., grandparent, grandchild, aunt/uncle, niece/nephew or first cousin.

3rd Degree Relative:
A relative removed by two generations, e.g., great-grandparent, great-grandchild, great-aunt/uncle, grandniece/nephew or second cousin.
GENETIC TESTING FOR CARDIAC ION CHANNELOPATHIES (cont.)

Definitions: (cont.)

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.

Schwartz Criteria:
A commonly used diagnostic scoring system for LQTS. A score of 4 or greater indicates a high probability that LQTS is present; a score of 2 to 3, a moderate-to-high probability; and a score of 1 or less indicates a low probability of the disorder.

<table>
<thead>
<tr>
<th>Schwartz Criteria</th>
<th>Points</th>
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<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
</tr>
<tr>
<td>• QT corrected greater than 480 ms</td>
<td>3</td>
</tr>
<tr>
<td>• QT corrected 460-470 ms</td>
<td>2</td>
</tr>
<tr>
<td>• QT corrected less than 450 ms</td>
<td>1</td>
</tr>
<tr>
<td>History of torsades de pointes</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T-waves in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>• Syncope brought on by stress</td>
<td>2</td>
</tr>
<tr>
<td>• Syncope without stress</td>
<td>1</td>
</tr>
<tr>
<td>• Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>• Family members with definite long QT syndrome</td>
<td>1</td>
</tr>
<tr>
<td>• Unexplained sudden death in immediate family members less than 30 years of age</td>
<td>0.5</td>
</tr>
</tbody>
</table>
GENETIC TESTING FOR CARDIAC ION CHANNELOPATHIES (cont.)

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.

Congenital Long QT Syndrome (LQTS):

- Genetic testing and/or counseling is considered medically necessary for an individual with suspected congenital LQTS who does not meet the clinical criteria for LQTS (e.g., Schwartz score less than 4) with documentation of ALL of the following:
  1. Moderate-to-high pretest probability of LQTS based on the Schwartz score and/or other clinical criteria
  2. Signs and symptoms of LQTS are present.

- Genetic testing and/or counseling for LQTS Large Deletion/Duplication mutation, is considered medically necessary for an affected individual with documentation of ALL of the following:
  1. Individual meets the above criteria for congenital LQTS testing
  2. Testing for congenital LQTS mutations is negative or inconclusive.

- Genetic testing and/or counseling for an individual with suspected congenital LQTS 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,
  2. Insufficient evidence to support improvement of the net health outcome,
  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:

- To determine prognosis and/or direct therapy in individuals with known LQTS
GENETIC TESTING FOR CARDIAC ION CHANNELOPATHIES (cont.)

Criteria: (cont.)

**Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):**

- Genetic testing and/or counseling is considered *medically necessary* for an individual with suspected CPVT when signs and/or symptoms of CPVT are present.

- Genetic testing and/or counseling for an individual with suspected CPVT 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,
  2. Insufficient evidence to support improvement of the net health outcome,
  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.

**Brugada Syndrome:**

- Genetic testing and/or counseling is considered *medically necessary* for an individual with suspected Brugada syndrome (BrS) with documentation of ANY of the following signs or symptoms of BrS:
  1. BrS characteristic electrocardiographic pattern in a family member
  2. Inducible ventricular arrhythmias on electrophysiologic studies
  3. Nocturnal agonal respirations
  4. Presence of a type 1 Brugada pattern on an electrocardiogram (ECG)
  5. Sudden cardiac death in a family member younger than 45 years old
  6. Syncope
  7. Ventricular arrhythmia

- Genetic testing and/or counseling for an individual with suspected BrS 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,
  2. Insufficient evidence to support improvement of the net health outcome,
  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 CARDIAC ION CHANNELOPATHIES (cont.)

Criteria: (cont.)

- Genetic testing and/or counseling for cardiac ion channelopathies 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,
  2. Insufficient evidence to support improvement of the net health outcome,
  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:

- Genetic testing for short QT syndrome

1 Determining the pretest probability of LQTS is not standardized. An example of an individual with a moderate-to-high pretest probability of LQTS is a Schwartz score of 2 or 3.

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 02/18/14 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


GENETIC TESTING FOR CARDIAC ION CHANNELOPATHIES (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/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 haada yit’éego bina’idiíldigí éí doodago Háida bighí anílyeedígíí t’aadoo le’é yina’idiíldigí beehaz’aanii hólo díí t’aá hazaad’ehjí háká a’doolwolgo bee haza’q doo baqh ilílnígó. Ata’háine’ígí kojí bích’jí hodilíinh 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. Đề nghị chuyển với một thông dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تتبعCanon أجهزة مخصصة الورقية، يجدر بالذكر أن كود Canon إلا لم تكن متوفرة على بعض الخدمات والمعلومات، 877-475-4799.
GENETIC TESTING FOR CARDIAC ION CHANNELOPATHIES (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, 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 makaasap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 무담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 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: اگر شما یا کسی که شما به آن کمک می‌کنید، سوال در مورد اطلاعاتی که در مورد Blue Cross Blue Shield of Arizona می‌توانید دریافت نمایید. 877-475-4799.

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

Serbo-Croatian: Ukoliko Vi ili neko kom 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: หากคุณ หรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสมควรจะได้รับความช่วยเหลือและข้อมูลภาษา ของคุณโดยไม่เสียค่าใช้จ่าย โปรดโทรต่อ โทร 877-475-4799.