GENETIC TESTING FOR EPILEPSY

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.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

Description:

Epilepsy is a disorder characterized by unprovoked seizures. It encompasses many different types of seizures and varies in age of onset and severity. Many genetic epilepsies are thought to have a complex, multifactorial genetic basis. There are also numerous rare epileptic syndromes that occur in infancy or early childhood, and that may be caused by single gene pathogenic variants. Genetic testing is being investigated for a large number of genetic genes that may be related to epilepsy.
GENETIC TESTING FOR EPILEPSY (cont.)

Description: (cont.)

Because of the large number of potential genes, panel testing is available from a number of genetic companies. These panels include a variable number of genes that have been implicated in diverse disorders. Some panels are designed to be comprehensive while other panels were developed for specific subtypes of epilepsy.

Examples of commercially available genetic panels for epileptic encephalopathies are listed below.

Panel tests include:
- GeneDx®: Infantile Epilepsy Panel
- MNG: Epileptic Encephalopathy
- University of Chicago Genetic Services: Early Infantile Epileptic Encephalopathy
- Athena Diagnostics Epilepsy Advanced Sequencing Evaluation

Single Genes Associated With Epileptic Syndromes:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome (also known as severe myoclonic epilepsy in infancy (SMEI) or polymorphic myoclonic epilepsy in infancy (PMEI))</td>
<td>SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CHD2, HCN1</td>
</tr>
<tr>
<td>Epilepsy limited to females with mental retardation (EFMR) syndrome</td>
<td>PCDH19</td>
</tr>
<tr>
<td>Epileptic encephalopathy with continuous spike-and-wave during sleep</td>
<td>GRIN2A</td>
</tr>
<tr>
<td>Genetic epilepsy with febrile seizures plus (GEFS+)</td>
<td>SCN1A, SCN9A</td>
</tr>
<tr>
<td>Early infantile epileptic encephalopathy (EIEE) with suppression burst (also known as Ohtahara syndrome)</td>
<td>KCNQ2, SLC25A22, STXBP1, CDKL5, ARX</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td>GRIN2A</td>
</tr>
<tr>
<td>West syndrome</td>
<td>ARX, TSC1, TSC2, CDKL5, ALG13, MAGI2, STXBP1, SCN1A, SCN2A, GABA, GABRB3, DNM1</td>
</tr>
<tr>
<td>Glucose transporter type 1 deficiency syndrome</td>
<td>SLC2A1</td>
</tr>
</tbody>
</table>
GENETIC TESTING FOR EPILEPSY (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.
GENETIC TESTING FOR EPILEPSY (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.

- Genetic testing and/or counseling of an affected individual for genes associated with infantile and early childhood-onset epilepsy syndrome is considered medically necessary with documentation of ALL of the following:
  1. Epilepsy is the core clinical symptom
  2. Seizure onset before the age of 5 years
  3. Clinically severe seizures that affect daily functioning and/or interictal EEG abnormalities
  4. No other clinical syndrome that would better explain symptoms
  5. Positive test result will lead to changes in ANY of the following:
     - Medication management agrees with MPRM
     - Diagnostic testing (i.e., avoidance of potentially invasive tests)
     - Reproductive decision making

These epilepsy syndromes include, but are not limited to:

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy [SMEI] or polymorphic myoclonic epilepsy in infancy [PMEI])
- Epilepsy limited to females with mental retardation (EFMR) syndrome
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- Early infantile epileptic encephalopathy with suppression burst (EIEE) syndrome, also known as Ohtahara syndrome
- Genetic epilepsy with febrile seizures plus (GEFS+) syndrome
- Glucose transporter type 1 deficiency syndrome
- Landau-Kleffner syndrome
- West syndrome
GENETIC TESTING FOR EPILEPSY (cont.)

Criteria: (cont.)

- Genetic testing for epilepsy 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.

Resources:

Literature reviewed 12/15/15. 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 EPILEPSY (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 níllíngíí Blue Cross Blue Shield of Arizona haada yī’ęgo bíná’ídílkidgo éí doodago Háída bíjá aníyeedígíí táadood le’ę yína’ídílkidgo beehaz’áanii hóló díí t’áá hazaadk’ehíí háká a’doowolgo bee haz’a doo baaq ilínígóó. Ata’ halné’ígíí kojí bíchí’é hódíllihíí 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 thợ dịch viễn, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تسامح أسئلة بخصوص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل ب. 877-475-4799.
GENETIC TESTING FOR EPILEPSY (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutuuanan, ay ma gaya karon tungkol sa Blue Cross Blue Shield of Arizona, ma payat aha an makakuhang mga tulong at impormasyon sa iyong wiya ng walong gastos. Upang makuasaap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 퀘어 또는 퀘어가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 퀘어는 그러한 도움과 정보를 퀘어의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그럴게 퀘어의 애플리케이션에서는 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:

انگر شما، یا کسی که شما به یا کمک می‌خواهید، سوال‌های مورد اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799.

Assyrian:

Blue Cross Blue Shield of Arizona

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

Thai: หากคุณ หรือผู้ที่คุณช่วยเหลืออยู่มีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ที่จะได้รับความช่วยเหลือและข้อมูลในภาษาของคุณโดยไม่เสียค่าใช้จ่าย โทร 877-475-4799.