GENETIC TESTING FOR MITOCHONDRIAL 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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**Description:**

Mitochondria are organelles within each cell that contain their own set of DNA, distinct from the nuclear DNA that makes up the majority of the human genome. Human mitochondrial DNA (mtDNA) consists of 37 genes and is inherited only from maternal DNA. Therefore, disorders that result from variants in mtDNA can only be passed on by the mother.
GENETIC TESTING FOR MITOCHONDRIAL DISORDERS (cont.)

Description: (cont.)

Mitochondrial disorders include:

- Chronic progressive external ophthalmoplegia (CPEO)
- Growth retardation, aminoaciduria, cholestasis, iron overload, early death (GRACILE)
- Infantile onset spinal cerebellar atrophy (IOSCA)
- Kearns-Sayre (KSS) syndrome
- Leigh syndrome (LS)
- Lieber’s hereditary optic neuropathy (LHON)
- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome
- Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)
- Sensory ataxia, neuropathy, dysarthria and ophthalmoplegia (SANDO)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Clinical Manifestations</th>
<th>Major Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELAS</td>
<td>Lactic acidosis</td>
<td>MT-TL1, MT-ND5 (&gt;95%)</td>
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<tr>
<td></td>
<td>Pigmentary retinopathy</td>
<td>MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS1, MT-TS2, MT-ND1, MT-ND6 (rare)</td>
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<tr>
<td></td>
<td>Seizures and/or dementia</td>
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<tr>
<td></td>
<td>Stroke-like episodes at age &lt;40</td>
<td></td>
</tr>
<tr>
<td>MERFF</td>
<td>Cerebellar ataxia</td>
<td>MT-TK (&gt;80%)</td>
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<tr>
<td></td>
<td>Myoclonus</td>
<td>MT-TF, MT-TP (rare)</td>
</tr>
<tr>
<td></td>
<td>Myopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
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<tr>
<td>CPEO</td>
<td>Bilateral ptosis</td>
<td>Various deletions of MT-DNA</td>
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<tr>
<td></td>
<td>External ophthalmoplegia</td>
<td></td>
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<tr>
<td>KSS</td>
<td>Cerebellar ataxia</td>
<td>Various deletions of MT-DNA</td>
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<tr>
<td></td>
<td>External ophthalmoplegia at age &lt; 20</td>
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<tr>
<td></td>
<td>Heart block</td>
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<tr>
<td></td>
<td>Pigmentary retinopathy</td>
<td></td>
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<tr>
<td>LS</td>
<td>Infantile onset</td>
<td>MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3</td>
</tr>
<tr>
<td></td>
<td>Cerebellar/brain stem dysfunction</td>
<td>MT-DNA deletions (rare)</td>
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<tr>
<td></td>
<td>Subacute relapsing encephalopathy</td>
<td>SUCLA2, NDUSFx, NDFVx, SDHA, BCS1L, SURF1, SCO2, COX15</td>
</tr>
<tr>
<td>LHON</td>
<td>Cardiac pre-excitation syndromes</td>
<td>MT-ND1, MT-ND4, MT-ND6</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
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<td></td>
<td>Male predominance</td>
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<td></td>
<td>Painless bilateral visual failure</td>
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<tr>
<td>NARP</td>
<td>Ataxia</td>
<td>MT-ATP6</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
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<td></td>
<td>Pigmentary retinopathy</td>
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</tbody>
</table>
GENETIC TESTING FOR MITOCHONDRIAL DISORDERS (cont.)

Description: (cont.)

Mitochondrial disorders include: (cont.)

<table>
<thead>
<tr>
<th>Syndrome (cont.)</th>
<th>Main Clinical Manifestations (cont.)</th>
<th>Major Genes Involved (cont.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNGIE</td>
<td>• Intestinal malabsorption&lt;br&gt;• Cachexia&lt;br&gt;• External ophthalmoplegia&lt;br&gt;• Neuropathy</td>
<td>• TP</td>
</tr>
<tr>
<td>IOSCA</td>
<td>• Ataxia&lt;br&gt;• Hypotonia&lt;br&gt;• Athetosis&lt;br&gt;• Ophthalmoplegia&lt;br&gt;• Seizures</td>
<td>• TWINKLE</td>
</tr>
<tr>
<td>SANDO</td>
<td>• Ataxic neuropathy&lt;br&gt;• Dysarthria&lt;br&gt;• Ophthalmoparesis</td>
<td>• POLG</td>
</tr>
<tr>
<td>Alpers syndrome</td>
<td>• Intractable epilepsy&lt;br&gt;• Psychomotor regression&lt;br&gt;• Liver disease</td>
<td>• POLG, DGUOK, MPV17</td>
</tr>
<tr>
<td>GRACILE</td>
<td>• Growth retardation&lt;br&gt;• Aminoaciduria&lt;br&gt;• Cholestasis&lt;br&gt;• Iron overload&lt;br&gt;• Lactic acidosis</td>
<td>• NDUSFx</td>
</tr>
<tr>
<td>Coenzyme Q10 deficiency</td>
<td>• Encephalopathy&lt;br&gt;• Steroid-resistant nephrotic syndrome&lt;br&gt;• Hypertrophic cardiomyopathy&lt;br&gt;• Retinopathy&lt;br&gt;• Hearing loss</td>
<td>• COQ2, COQ9, CABC1, ETFDH</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.

Gene Expression:
The translation of the information encoded in a gene into messenger RNA (mRNA) which may or may not then be translated into a protein.

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:

- 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 to establish a genetic diagnosis of a mitochondrial disorder is considered medically necessary when signs and symptoms of a mitochondrial disorder are present and genetic testing may eliminate the need for muscle biopsy.
GENETIC TESTING FOR MITOCHONDRIAL DISORDERS (cont.)

Criteria: (cont.)

- Genetic testing for mitochondrial disorders 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 07/18/17. 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.

GENETIC TESTING FOR MITOCHONDRIAL 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 nilínígíí Blue Cross Blue Shield of Arizona haadá yit’éégo bina’ídi’díkído éí doodago Háída bii’yí anilyeedííí t’áadoo le’éé yina’ídíkído beehaz’aaní hólo díí t’áá hazaadd’ehíí háká a’doowolgo bee haza’ doo báah ilínígóó. A’ta’ halne’ííí kójí bíchí’í’ hodiilnhíi 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 thể 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 لدى شخص تساعدك أسئلة بخصوص Blue Cross Blue Shield of Arizona الهام، قم بمكالمة مترجم أو مترجمة. للتحدث مع مترجم الأصل ب 877-475-4799.
GENETIC TESTING FOR MITOCHONDRIAL 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 makuasaang ang isang tagsaluy, tumawag ka sa 877-475-4799.

Korean: 안녕히 계시는 분들께 이 메시지를 전해드리며 Blue Cross Blue Shield of Arizona에 관한 문의가 있거나, 문의하시는 내용에 대한 도움과 정보를 제공하기 위하여 사용 가능한 언어로 접수, 답변이 가능한 서비스가 있습니다. 그림으로 이메일을 주시시오.

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。通訳をお話される場合、877-475-4799までお電話ください。

Farsi:

اگر شما، یا کسی که شما به او کمک می‌کنید، سوال نوزودعات و اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799.

Assyrian:

B Blue Cross Blue Shield of Arizona

Serbo-Croatian: Ukoliko Vi ili neko kom 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 prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสามารถได้รับความช่วยเหลือและข้อมูลในภาษาของคุณโดยไม่ผ่านไปทาง โทร 877-475-4799