GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA

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 FAMILIAL HYPERCHOLESTEROLEMIA (cont.)

Description:

Familial hypercholesterolemia (FH) is an inherited disorder categorized as heterozygous (inherited from one parent) or homozygous (inherited from both parents). FH may be caused by mutations in the LDL receptor (LDLR), apolipoprotein B (apo-B) and proprotein convertase subtilisin kexin type 9 (PCSK9) genes.

FH is characterized by a high LDL-C level from birth, relatively normal high-density lipoprotein (HDL-C) and triglycerides, and early-onset coronary heart disease. Findings of FH on physical examination may include arcus corneae (a white ring around the cornea), xanthelasma (sharply demarcated yellowish deposits of fat underneath the skin) and tendon or tuberous xanthomas.

Heterozygous Familial Hypercholesterolemia (HeFH):
HeFH is more common than homozygous FH, with an estimated prevalence between 1 in 300 to 1 in 500 individuals. The average age for presentation with coronary artery disease (CAD) is in the fourth decade for males and the fifth decade for females, and there is a 30% to 50% increase in risk for men and women in the fifth and sixth decades, respectively. Individuals with HeFH can present with total cholesterol in the range of 350-550 mg/dL.

Homozygous Familial Hypercholesterolemia (HoFH):
HoFH is more severe than HeFH with an estimated prevalence of 1 in 1,000,000. The average age for presentation with coronary artery disease (CAD) is in the second or third decade. Individuals with HoFH can present with total cholesterol in the range of 650-1000 mg/dL.

Diagnosis of Definitive and Uncertain FH:

The diagnosis of FH relies on elevated LDL levels in conjunction with a family history of premature CAD and physical exam signs of cholesterol deposition. There is wide variability in cholesterol levels for individuals with FH and physical exam findings may not be specific enough. Because of the variable cholesterol levels and the low sensitivity of physical exam findings, there are a considerable number of individuals in whom the diagnosis is uncertain. For these individuals, there are a number of formal diagnostic tools for determining the definitive diagnosis of FH.

When FH is suspected and evaluated against the following standardized diagnostic criteria, it can be interpreted that the individual is in an “uncertain” category when these criteria for a definitive diagnosis are not met.
GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA (cont.)

Description: (cont.)

Dutch Lipid Clinic Criteria:
- Criteria assigns points for family history, CAD in the individual, physical exam signs of cholesterol deposition and LDL levels.
- Diagnosis of definitive FH is made when the score is 8 or higher.
- Diagnosis of possible or probable FH is made when the score is 3 to 7.
- Diagnosis of possible or probable FH represents “uncertain” FH.

Make Early Diagnosis Prevent Early Deaths Program Diagnostic Criteria (MEDPED):
- Criteria provides a yes/no answer for a definitive diagnosis of FH based on family history, age and cholesterol levels.
- An individual who meets criteria for FH can be considered to have definitive FH.
- There is no possible or probable category that allows assignment of an “uncertain” category.

Simon Broome Criteria:
- Diagnosis of definitive FH is made based on a total cholesterol level greater than 290 mg/dL in adults (or low-density lipoprotein greater than 190 mg/dL) and either 1) positive physical exam findings or 2) positive genetic test.
- Diagnosis of probable FH is based on a total cholesterol level greater than 290 mg/dL in adults (or low-density lipoprotein greater than 190 mg/dL) and either 1) family history of premature CAD or 2) total cholesterol of at least 290 mg/dL in a first- or a second-degree relative.
- Diagnosis of probable FH represents “uncertain” FH.
Definitions:

Adult: Age 18 years and older

Genetic Testing:
Analysis of DNA, RNA, chromosomes, proteins and certain metabolites in order to detect alterations related to an inherited disorder.

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.

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.

Familial Assessment:
1st, 2nd, and 3rd degree relatives are blood relatives on the same side of the family (maternal or paternal).

- 1st Degree Relative: Blood-related sibling, parent or child.
- 2nd Degree Relative: Blood-related relative removed by one generation, e.g., grandparent, grandchild, aunt/uncle, niece/nephew or half siblings.
- 3rd Degree Relative: Blood-related relative removed by two generations, e.g., great-grandparent, great-grandchild, great-aunt/uncle, grandniece/nephew or first cousin.
GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA (cont.)

Criteria:

**Heterozygous Familial Hypercholesterolemia (HeFH):**

- Genetic testing and/or counseling of an unaffected adult, 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 to confirm a diagnosis of HeFH is considered medically necessary when a definitive diagnosis is required as an eligibility criterion for specialty medications with documentation of **ALL** of the following:
  1. Genetic testing is targeted to individuals who are in an uncertain category category (see Description section) according to clinical criteria (personal and family history, physical exam, lipid levels)
  2. Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test

- Genetic testing and/or counseling of children of individuals with HeFH to determine future risk of disease is considered medically necessary with documentation of **ALL** of the following:
  1. A pathogenic variant is present in a parent
  2. General lipid screening is not recommended based on age or other factors

- Genetic testing and/or counseling to confirm a diagnosis of HeFH 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.
GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA (cont.)

Criteria: (cont.)

Homzygous Familial Hypercholesterolemia (HoFH):

- Genetic testing and/or counseling of an unaffected adult, 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 to confirm a diagnosis of HoFH is considered medically necessary when a definitive diagnosis is required as an eligibility criterion for specialty medications with documentation of ALL of the following:
  1. Genetic testing is targeted to individuals who are in an uncertain category (see Description section) according to clinical criteria (personal and family history, physical exam, lipid levels)
  2. Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test

- Genetic testing and/or counseling of children of individuals with HoFH to determine future risk of disease is considered medically necessary with documentation of ALL of the following:
  1. A pathogenic variant is present in both parents
  2. General lipid screening is not recommended based on age or other factors

- Genetic testing and/or counseling to confirm a diagnosis of HoFH 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.
GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA (cont.)

Resources:

Literature reviewed 11/28/17. 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 FAMILIAL HYPERCHOLESTEROLEMIA (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 níilígíí Blue Cross Blue Shield of Arizona haadá yít’éego bina’ídílíkidgo éí doodago Háida bįį anilyeedííí t’aadoo le’e yina’ídílíkidgo beehaz’áanii hóló dií t’áa házaadk’ehíi háká a’doowolgo bee haz’á doo bąáqh ilínígóó. Ata’ halne’ídíí kojí bích’įį hodíííníh 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 thông dịch viên, xin gọi 877-475-4799.

Arabic: إن كنت تريد أو أدى شخص تساعده أسلطة بخصوص

الضرورية بِلغتك من دون اية تكلفة، للتحدث مع مترجم اتصل ب 877-475-4799.
GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA (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: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 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 tout 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:
آگر شما، یا کسی که شما به آن کمک می‌کنید، سوال‌های مربوط به Blue Cross Blue Shield of Arizona دارید یا به آن کمک می‌کنید، به تلفون 877-475-4799 می‌توانید به یک مترجم تماس بگیرید.

Assyrian:
لا باب، تو یا مایعی که تو می‌تونی به او کمک کنی، سوال‌نونو متعلق به Blue Cross Blue Shield of Arizona ناشی می‌شود یا تو به او کمک می‌کنی، به تلفون 877-475-4799 می‌تونی با یک دیپلمات صحبت کنی.

Serbo-Croatian: Ukoiko 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 คุณมีสิทธิ์ที่จะได้รับความช่วยเหลือและข้อมูลในภาษาของคุณโดยไม่ต้องเสียค่าใช้จ่าย โปรดโทรตามที่ 877-475-4799.