GENETIC TESTING FOR LYOSOMAL ACID LIPASE DEFICIENCY (LAL-D)

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.
GENETIC TESTING FOR LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) (cont.)

Description:

**Lysosomal Acid Lipase Deficiency (LAL-D):** LAL-D is a rare autosomal recessive genetic disorder caused by a deleterious mutation to the LIPA gene responsible for encoding the enzyme lysosomal lipase resulting in a marked decrease or loss of LAL enzyme activity. The defective enzyme activity results in a progressive accumulation of cholesteryl esters and triglycerides in hepatocytes, adrenal glands, intestines, and cells of the macrophage-monocyte system. LAL-D may manifest from infancy to adulthood as 1 of 2 phenotypes, Wolman disease (WD) or Cholesteryl ester storage disease (CESD). Both presentations have come to be known as LAL-D. Diagnosis of LAL deficiency is confirmed by identification of either biallelic pathogenic variants in the LIPA gene or deficient LAL enzyme activity.

**Cholesteryl Ester Storage Disease (CESD):** The late onset phenotype of LAL-D has been reported in individuals who are less than 1 year to more than 60 years of age. They can present as a wide range of phenotypes. Individuals with CESD can be asymptomatic into adulthood and have life-threatening conditions similar to WD in infancy. Individuals typically have lipid abnormalities, hepatomegaly, splenomegaly, and gastrointestinal symptoms.

**Lysosomal Acid Lipase Deficiency Testing:** Diagnosis is confirmed by identification of deficient LAL enzyme activity in peripheral blood leukocytes, fibroblasts, or dried blood spots. Molecular testing approaches can include single-gene testing or use of a multi-gene panel. For single-gene testing, sequence analysis of the LIPA gene is performed first. Gene targeted deletion/duplication analysis is considered if only one pathogenic variant is identified. A multi-gene panel to include the LIPA gene may be considered. The exon 8 splice site mutation (E8SJM) is the most common variant identified. Greater than 40 mutations in the LIPA gene have been reported.

**Wolman Disease (WD):** The early onset phenotype and most progressive form of LAL-D occurs during early infancy. WD typically presents in the first weeks of life resulting in multi-organ failure seldom living beyond 6 months of age. Individuals typically have prominent hepatosplenomegaly, diarrhea, vomiting, malabsorption, growth failure, and liver failure.
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.

Criteria:

For treatment of lysosomal acid lipase deficiency with Kanuma™, see BCBSAZ Medical Coverage Guideline #O992, “Kanuma™ (sebelipase alfa)”.

Genetic Testing for Lysosomal Acid Lipase Deficiency will be reviewed by the medical director(s) and/or clinical advisor(s).

- 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 FOR LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) (cont.)

Criteria: (cont.)

- Genetic testing and/or counseling for LAL-D is considered medically necessary for an affected individual to identify the causative LIPA gene mutation with documentation that a definitive diagnosis was not confirmed by ONE of the following:

  1. LDL-C concentration of 4.7 mmol/L or greater (or > 181 mg/dL) and family history evaluation establishes an autosomal dominant pattern of inheritance
  2. LDL-C concentration of 4.7 mmol/L or greater (or > 181 mg/dL) and family history evaluation establishes a recessive pattern of inheritance and documentation of ALL of the following:

     •   THREE or more of the following:

       a. ALT level greater than 1.5 of the upper limit of normal
       b. HDL-C level less than 1.3 mmol/L (or < 50 mg/dL)
       c. Body mass index of 30 kg/m² or more
       d. Liver biopsy suggestive of microvesicular steatosis
       e. Hepatomegaly

     •   ONE of the following:

       a. Dried blood spot test results positive for LAL activity
       b. Dried blood spot test results borderline for LAL activity and ONE of the following genetic testing results:

           - Positive for the Exon 8 splice site mutation (E8SJM)
           - Negative for the E8SJM and genetic testing of the LIPA gene identified the causative mutation for LAL-D

  3. Prescribed by a physician with experience in the care of individuals with LAL-D

- Genetic testing and/or counseling for LAL-D 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 LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) (cont.)

Resources:

Literature reviewed 08/27/18. We do not include marketing materials, poster boards and non-published literature in our review.


GENETIC TESTING FOR LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) (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 níilíngíí Blue Cross Blue Shield of Arizona haadá yít’éego bina’ídilkidgo éí doodago Háída bijá anílyeedígíí t’áaddoo le’é yína’ídilkidgo beehaž’áánii hólo díí t’áá hazaak’éhíí háká a’doooolgo bee ha’á doo báqah ilínígóó. Ata’ halne’ígíí kójí bích’íí hodilínhíí 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 كان لديك أو أداء شخص يساعدك شخصًا يكون موصولًا بخصوص Blue Cross Blue Shield of Arizona الفضري عن طريق تنفيذ او تلقي معلومات، للاستفادة من دليلا تكلفة. للتحدث مع مترجم السلا ب 877-475-4799.
GENETIC TESTING FOR LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) (cont.)

Multi-Language Interpreter Services: (cont.)

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

Korean: 만약 궁할 또는 궁할을 들고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 궁할을 들고 있는 영어로 비용 부담 없이 읽을 수 있는 권리가 있습니다. 그렇게 투영시와 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 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:

آگر شما، یا کسی به شما به یا کمک می‌خواهد، سوالی در مورد اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799.

Assyrian:

BlueCross Blue Shield of Arizona یک شرکت جهانی و تحقیقاتی و خدماتی و کمک‌های جهانی، است. گزارش‌های مالی، مالی و خدماتی 877-475-4799.

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 prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือผู้ที่ช่วยเหลือผู้ป่วย欢迎您 Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ที่จะได้รับความช่วยเหลือและข้อมูลภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 877-475-4799.