



MEDICAL COVERAGE GUIDELINES  
SECTION: LABORATORY

ORIGINAL EFFECTIVE DATE 10/13/15  
LAST REVIEW DATE: 10/16/18  
LAST CRITERIA REVISION DATE:  
ARCHIVE DATE:

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## NOVEL BIOMARKERS IN RISK ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASE

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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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## **NOVEL BIOMARKERS IN RISK ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASE (cont.)**

### **Description:**

Numerous lipid and nonlipid biomarkers have been investigated as potential risk assessment tools for cardiovascular disease.

### **Lipid Biomarkers:**

#### **Apolipoprotein A-1 (apo A-1):**

Apo A-1 is a component of all HDL particles. Direct measurement of apo A-1 has been investigated as an adjunct to high-density lipoprotein (HDL) measurement. The ratio of apo B/apo A-1 has been proposed to measure the ratio of “bad cholesterol” to “good cholesterol.”

#### **Apolipoprotein B (apo B):**

Apo B is the major protein in all lipoproteins except (HDL). Direct measurement of apo B has been investigated as an adjunct to low-density lipoprotein (LDL) measurement. The ratio of apo B/apo A-1 has been proposed to measure the ratio of “bad cholesterol” to “good cholesterol.”

#### **Apolipoprotein E (apo E):**

Apo E, which has 6 different genotypes, is a component of very low-density lipoproteins (VLDL) and is thought to play an important role in lipid metabolism. Apo E has been investigated in the selection and response of lipid lowering medications.

#### **HDL Subclass:**

HDL plays a protective role against CAD. There are five categories of HDL particles based upon their size. HDL particle size and/or number can be directly measured using nuclear magnetic resonance (NMR) spectroscopy. Measurement of HDL subclasses has been investigated to provide additional information on cardiovascular risk compared to HDL alone.

#### **LDL Subclass:**

There are 2 major subclass patterns of LDL based on particle diameter and density. In subclass pattern A, the particles have a diameter larger than 25 nm and are less dense. In subclass pattern B, the particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a commonly inherited disorder associated with a more atherogenic lipoprotein profile, also termed “atherogenic dyslipidemia.” In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apolipoprotein B, and low levels of HDL. Measurement of LDL subclasses has been investigated as a component of metabolic syndrome, to predict cardiac risk and to monitor treatment response.

LDL particle (LDL-P) concentration can be directly measured using NMR spectroscopy. The NMR LipoProfile® Test has been investigated as an additional technique to predict cardiac risk.

#### **Lipoprotein A (lp[a]):**

Lp(a) is similar to LDL and structurally similar to plasminogen. Measurement of lp(a) has been investigated as a link between atherosclerosis and thrombosis.



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## NOVEL BIOMARKERS IN RISK ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASE (cont.)

Description: (cont.)

### Nonlipid Biomarkers:

#### B-Type or Brain Natriuretic Peptide (BNP):

BNP is an amino acid polypeptide which is secreted primarily by the ventricles of the heart when pressure to the cardiac muscles increases or there is myocardial ischemia. Elevations in BNP levels reflect deterioration in cardiac loading levels and may predict adverse events. BNP has been investigated as a biomarker for predicting cardiovascular and heart failure risk.

#### Cystatin C:

Cystatin C is a small serine protease inhibitor protein that is secreted from all functional cells found throughout the body. It has primarily been used as a biomarker of kidney function. Cystatin C has also been investigated to determine whether it may serve as a biomarker for predicting cardiovascular risk. Cystatin C is encoded by the CST3 gene.

#### Fibrinogen:

Fibrinogen is a circulating clotting factor and precursor of fibrin. It is important in platelet aggregation and a determinant of blood viscosity. Fibrinogen levels have been investigated and shown to be associated with future risk of cardiovascular risk and all-cause mortality.

#### Leptin:

Leptin is a protein secreted by fat cells that has been found to be elevated in heart disease. Leptin has been investigated to determine if it has any relationship with the development of cardiovascular disease.



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## NOVEL BIOMARKERS IN RISK ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASE (cont.)

### Criteria:

- Measurement of novel lipid and nonlipid risk as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease 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.

Biomarkers include, *but are not limited to*:

- Apolipoprotein A-1 (apo A-1)
- Apolipoprotein B (apo B)
- Apolipoprotein E (apo E)
- B-type natriuretic peptide
- Cystatin C
- Fibrinogen
- HDL subclasses
- Leptin
- LDL subclasses
- Lipoprotein A (lp[a])

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### Resources:

Literature reviewed 10/16/18. 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 10/13/15 may be requested from the BCBSAZ Medical Policy and Technology Research Department.

1. 2.04.65 BCBS Association Medical Policy Reference Manual. Novel Lipid Risk Factors in Risk Assessment and Management of Cardiovascular Disease. Re-issue date 02/08/2018, issue date 06/10/2010.



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## NOVEL BIOMARKERS IN RISK ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASE (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](mailto: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 nilinígíí Blue Cross Blue Shield of Arizona haada yit'éego bina'idilkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yina'idilkidgo beehaz'áanii hólo díí t'áa hazaadk'ehjí háká a'doowołgo bee haz'ą doo baqah ilinígóó. Ata' halne'ígíí kojį' bich'į' hodilnih 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 لدى شخص تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل بـ 877-475-4799.

