GENETIC AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER

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 AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER (cont.)

**Description:**

There are a variety of genetic and protein biomarkers associated with prostate cancer. Testing for these biomarkers has been investigated for improving the accuracy of differentiating which men should undergo prostate biopsy or repeat biopsy after an initial negative biopsy. Single nucleotide variant testing has also been investigated for cancer risk assessment. Testing may also be referred to as liquid biopsies.

The following genetic and protein biomarker tests have been investigated for the diagnosis and cancer risk assessment of prostate cancer:

**Apifiny® Prostate Cancer Test:**
Apifiny is a cancer specific, non-PSA blood test designed to aid in the risk assessment of prostate cancer. The Apifiny technology is based on the measurement of eight prostate cancer specific autoantibodies in the blood. These autoantibodies are produced and replicated (amplified) by the immune system in response to the presence of prostate cancer cells.

The Apifiny test process is performed in part using a qualitative immunoassay technique and in part using flow cytometry. The laboratory data generated by these methodologies are then subjected to a proprietary algorithmic analysis that generates a cancer risk score between zero and 100. When combined with other information (i.e., PSA level, PSA velocity, DRE, race, family history, etc.) men with lower risk Apifiny scores may be placed on a routine clinical monitoring program with other accepted methods to assess the ongoing risk of prostate cancer. Men with higher Apifiny scores may require a more specific risk assessment plan which may include referral to a specialist and/or a prostate biopsy.

**Candidate Gene Panels:**
Candidate gene panels combine several genetic and protein biomarkers into a single test to diagnose prostate cancer.

**ExosomeDx® Prostate (IntelliScore):**
The ExosomeDx Prostate (IntelliScore), also referred to as ExoDx® from Exosome Diagnostics, Inc. is a urine test that detects three genetic biomarkers to identify the aggressiveness of prostate cancer.

**Gene Hypermethylation Testing:**
ConfirmMDx® test is a blood test that measures hypermethylation of three genes (GSTP1, APC and RASSF1) to determine whether an individual should undergo repeat biopsy after an initial negative biopsy.

**Kallikrein Markers:**
4Kscore™ test is a blood test that measures four prostate specific kallikreins (total prostate-specific antigen [tPSA], free PSA [fPSA], intact PSA [iPSA] and human kallikrein 2 [hK2]) which are combined into an algorithm to select men for initial prostate biopsy and repeat prostate biopsy.
GENETIC AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER (cont.)

Description: (cont.)

Mitochondrial DNA Variant Testing:
The Prostate Core Mitomics Test™ uses existing tissue from a negative prostate biopsy to measure mitochondrial DNA variants to determine whether an individual should undergo repeat biopsy after an initial negative biopsy.

Prostate Cancer Antigen 3 (PCA3) Testing:
The Progensa® PCA3 Assay is a post-DRE urine test that measures PCA3 levels to determine whether an individual should undergo repeat biopsy after an initial negative biopsy.

Prostate Health Index (phi) Testing:
proPSA is a blood test that combines several components of PSA with an algorithm to calculate the phi. The phi is used as an aid in distinguishing prostate cancer from benign prostatic condition in men ages 50 and older with prostate-specific antigen level of 4 to 10 ng/mL and with DRE findings that are not suspicious. Test is used to select men for initial prostate biopsy or for repeat biopsy after an initial negative biopsy.

Reverse Transcription PCR (RT-PCR) Assay:
SelectMDx™ for Prostate Cancer is a RT-PCR assay performed on post-DRE first-void urine specimens from individuals with clinical risk factors for prostate cancer who are being considered for biopsy. The test measures the mRNA levels of the DLX1 and HOXC6 biomarkers, using KLK3 expression as internal reference. Higher expression levels of DLX1 and HOXC6 mRNA are associated with an increased probability for high-grade (Gleason score (GS) ≥ 7) prostate cancer.

Single-Nucleotide Variant (SNV) Testing:
Single-nucleotide variants occur when a single nucleotide is replaced with another. These variants are the most common type of genetic variation in humans. They occur normally throughout the genome and can act as biological markers for disease association. Genome-wide association studies have identified associations between prostate cancer risk and specific SNVs. However, it is generally accepted that individually, SNV-associated disease risk is low and of no value in screening for disease, although multiple SNVs in combination may account for a higher proportion of prostate cancer.

Transmembrane Serine Protease (TMPRSS) Testing:
TMPRSS testing is a post-digital rectal exam (DRE) test that detects fusion of the TMPRSS and EGR gene. TMPRSS2-ERG gene rearrangements have been reported in primary prostate cancer samples. TMPRSS fusion gene detection has been investigated as a method to identify aggressive disease or to predict disease recurrence. Fusion genes may be detected in tissue, serum or urine.
GENETIC AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER (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 AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER (cont.)

Criteria:

For gene expression profile analysis for prostate cancer management, see BCBSAZ Medical Coverage Guideline #0862, “Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management”.

- 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 and protein biomarkers and/or counseling for the diagnosis of prostate cancer are 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, and
  4. Insufficient evidence to support improvement outside the investigational setting.

These genetic and protein biomarkers include, but are not limited to:

- Apifiny Prostate Cancer Test
- Candidate gene panels
- ExosomeDx Prostate (IntelliScore) (e.g., ExoDx)
- Gene hypermethylation testing (e.g., ConfirmMDx)
- Kallikrein markers (e.g., 4Kscore Test)
- Mitochondrial DNA variant testing (e.g., Prostate Core Mitomics Test)
- PCA3 testing (e.g., Progensa)
- Prostate Health Index (phi)
- Reverse Transcription PCR (RT-PCR) Assay (e.g., SelectMDx for Prostate Cancer)
- TMPRSS fusion genes
GENETIC AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER  (cont.)

Criteria: (cont.)

- Single nucleotide variant testing for cancer risk assessment of prostate cancer is considered 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, and
  4. Insufficient evidence to support improvement outside the investigational setting.

Resources:

Literature reviewed 12/12/17. 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.

Resources prior to 01/07/14 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


GENETIC AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER (cont.)

Resources: (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: Sí 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 nilníígíí Blue Cross Blue Shield of Arizona haadá yít’éego bíná’díil’kidgo éé doodago Háida bijá aniiyeediíi t’aadoo le’é yíná’l’íilkidgo beeház’aánni hóó díí t’áá hazaad kéehi háká a’dooowol’go bee haz’a doo baah ilíngóó. Atá’ halné’ííiíi koj’í bích’í hodilíní h 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於補充項目的問題 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 thống dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعدته أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أي تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.
GENETIC AND PROTEIN BIOMARKERS FOR THE DIAGNOSIS AND CANCER RISK ASSESSMENT OF PROSTATE CANCER (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 makaasap 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 통해서 귀하가 필요하다면 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:

اگر شما، یا کسی که شما به او کمک می‌کنید، سوال در مورد اطلاعاتی به زبان خود را به من رایگان دریافت نمایید 877-475-4799.

Assyrian:

Blue Cross Blue Shield of Arizona ناممایه. ناسک دەواچی جێکەیە کە لەبەرەیەکان اوە دەبەکەیە لەبەرەیەکان. 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 dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodom, nazovite 877-475-4799.

Thai: หากคุณหรือคนที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสามารถขอรับความช่วยเหลือและข้อมูลในภาษา ของคุณได้โดยไม่ต้องเสียค่าใช้จ่าย ตลอดทุกวันโดยโทร 877-475-4799.