

Policy: MP273

Section: Medical Benefit Policy

Subject: Gene-based Testing and/or Protein Biomarkers for Diagnosis and Management of Prostate Cancer

I. Policy: Gene-based Testing and/or Protein Biomarkers for Diagnosis and Management of Prostate Cancer

II. Purpose/Objective:

To provide a policy of coverage regarding Gene-based Testing and/or Protein Biomarkers for Diagnosis and Management of Prostate Cancer

III. Responsibility:

- A. Medical Directors
- B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

- (i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
- (ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
- (iii) The service or benefit will assist the Member to achieve or maintain maximum functional

capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.

DESCRIPTION:

Prostate cancer antigen 3 (PCA3, also referred to as DD3) is a gene that expresses a non-coding RNA. PCA3 is only expressed in human prostate tissue, and the gene is highly overexpressed in prostate cancer. Because of its restricted expression profile, the PCA3 RNA is thought to be useful as a tumor marker. The PCA3 Assay is an automated molecular assay that helps physicians determine the need for repeat prostate biopsies in members who have had a previous negative biopsy.

In vitro gene expression prognostic assays measure gene expression in tumor tissue samples or from prostate biopsy samples to provide a personalized risk score indicative of a tumor's aggressiveness and may also provide a long-range prostate cancer -specific mortality risk score.

Epigenetic assays utilize methylation-specific PCR to assess DNA methylation of gene regions that are associated with prostate cancer. The test assesses the methylation status of glutathione s-transferase PI (GSTP1), adenomatous polyposis coli (APC), and RAS association (RalGDS/AF-6) domain family member 1 (RASSF1).

Prolaris® is a genomic test developed to aid physicians in predicting prostate cancer aggressiveness in conjunction with clinical parameters such as Gleason score and PSA. Prolaris® is a direct molecular measure of prostate cancer tumor biology. By measuring the expression levels of genes involved with cancer replication, Prolaris® is promoted as being able to more accurately predict disease progression. Oncotype Dx® Prostate Cancer Assay (Genomic Health, Redwood City, CA) is a gene expression profiling test that uses archived tumor specimens as the mRNA source, and reverse transcriptase polymerase chain reaction (RT-PCR) amplification to quantify expression levels of 12 cancer-related and 5 reference genes to generate a Genomic Prostate Score. Decipher® is a 22 gene expression profile test intended to guide who can delay or defer radiation after radical prostatectomy. Promark™ is an automated quantitative imaging method to measure protein biomarkers by immunofluorescent staining in formalin-fixed paraffin-embedded biopsy tissue. It is designed to provide prognostic information to help differentiate patients to active surveillance or therapy.

The National Comprehensive Cancer Network® (NCCN) guidelines for prostate cancer (v 1.2018) encourages physicians to consider molecular testing of a patient's tumor post-biopsy when prostate cancer presents as low- or favorable intermediate-risk and life expectancy is greater than or equal to 10 years.

COMMERCIAL and NON-MEDICARE BUSINESS SEGMENTS

ConfirmMDx is covered for members with negative or non-malignant abnormal histopathology findings, such as atypical cell or high-grade prostate intraepithelial neoplasia (HGPIN) on prostate biopsy, yet with high-risk factors (elevated/rising PSA or abnormal digital rectal exam) and are candidates for repeat biopsy

SelectMDx is covered when **all of the following** criteria are met:

1. The member is a candidate for prostate biopsy or repeat prostate biopsy, (NCCN criteria):
 - For men ≤ 75 years of age - Prostate Specific Antigen (PSA) (or adjusted PSA in special populations, i.e., patients taking 5alpha-reductase inhibitors) OR repeat PSA are >3 and <10ng/mL AND/OR Digital Rectal Exam (DRE) findings are very suspicious for cancer; **or**
 - For men > 75 years of age - PSA (or adjusted PSA in special populations, i.e., patients taking 5alpha-reductase inhibitors) OR repeat PSA are ≥4 and <10ng/mL AND/OR DRE findings are very suspicious for cancer

and

2. The member has not had a prostate biopsy OR has had a previous negative or non-malignant but abnormal histopathology finding (i.e., atypical small acinar proliferation or high-grade prostatic intraepithelial neoplasia (HGPIN) on prostate biopsy); **or**
Member is under consideration for a repeat biopsy have first undergone repeat PSA and/or DRE testing AND a repeat biopsy is considered within 24-months of the prior biopsy.

and

3. The test is ordered by a physician specialist in the management of prostate cancer, such as a urologist or oncologist.

Prolaris, OncoType Dx, Decipher:

Gene expression prognostic assay (eg, **Prolaris, OncoType Dx, Decipher**) is covered for members to help determine which members with early stage, needle biopsy proven prostate cancer can be conservatively managed rather than treated with definitive surgery or radiation therapy when **all of the following** criteria are met:

1. Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node

- involvement), **and**
2. Formalin fixed paraffin-embedded (FFPE) prostate biopsy specimen with at least 0.5 mm of cancer length; **and**
 3. Stage as defined by the one of the following:
 - Very Low Risk Disease (T1c AND Gleason Score \leq 6 AND PSA \leq 10 ng/mL AND $<$ 3 prostate cores with tumor AND \leq 50% cancer in any core AND PSA density of $<$ 0.15 ng/mL/g) **OR**
 - Low Risk Disease (T1-T2a AND Gleason Score \leq 6 AND PSA \leq 10 ng/mL), **and**
 4. The member has an estimated life expectancy of greater than or equal to 10 years, **and**
 5. The member is a candidate for and is considering conservative therapy and yet would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), **and**
 6. Result will be used to determine treatment between definitive therapy and conservative management.

OncoType DX AR-V7 assay is covered when **all of the following** criteria are met:

1. The member is diagnosed with progressive mCRPC as defined by the Prostate Cancer Working Group 2 guidelines (a minimum of 2 rising prostate-specific antigen (PSA) levels 1 or more weeks apart, new lesions by bone scintigraphy, and/or new or enlarging soft tissue lesions by computed tomography or magnetic resonance imaging; **and**
2. The member has experienced failure on one androgen receptor signaling inhibitor (ARSi), (e.g., Enzalutamide (Xtandi), Apalutamide (Erleada), or Abiraterone (Zytiga).; **and**
3. The member is considered to be appropriate for treatment by their treating physician for the alternative ARSi as a single agent; **and**
4. Circulating tumor cells with nuclear expression of AR-V7 protein will be assessed prior to initiation of therapy

4Kscore testing will be considered for coverage when **all of the following** criteria are met:

- A. The member is 45 years of age and older, prior to an initial biopsy or following a negative biopsy, who has a confirmed moderately elevated PSA defined as greater than 3 and less than 10 ng/mL; **or**
- B. The member is 75 years of age and older, prior to an initial biopsy or following a negative biopsy, who has a confirmed moderately elevated PSA defined as greater than or equal to 4 and less than 10 ng/mL

and BOTH of the following are present:

1. No other relative indication for prostate biopsy including **ANY** of the following: (this may not be an all-inclusive list):
 - DRE suspicious for cancer should be encouraged to undergo biopsy
 - Persistent and significant increase in PSA should be encouraged to undergo biopsy
 - Positive multiparametric magnetic resonance imaging (MRI) (if done)
 - Other major risk factor for prostate cancer including: (this may not be an all-inclusive list)
 - Ethnicity at higher risk for prostate cancer
 - First-degree relative with prostate cancer
 - High-penetrance prostate cancer risk gene(s) per the National Comprehensive Cancer Network (NCCN) (if known)
2. No other relative contraindication for prostate biopsy including **ANY** of the following:
 - Less than a 10 year life expectancy
 - Benign disease not ruled out.

MEDICARE BUSINESS SEGMENT:

PCA3 Assay (eg, Progenesa) is covered for members to help determine the need for repeat prostate biopsies in members who have had a previous negative biopsy.

Palmetto GBA a Medicare Administrative Contractor (MAC) that assesses molecular diagnostic technologies and establishes the coverage policy for Medicare beneficiaries has determined that **ConfirmMDx** is covered in members with previous negative prostate biopsy who are being considered for repeat biopsy when the following criteria are met:

- Males aged 40 to 85 years old that have undergone a previous cancer-negative prostate biopsy within 24 months and are being considered for a repeat biopsy due to persistent or elevated cancer-risk factors, and

- The previous negative prostate biopsy must have collected a minimum of 8 tissue cores (but not have received a saturation biopsy of > 24 tissue cores) and remaining FFPE tissue from all cores is available for testing, and
- Minimum tissue volume criteria of 20 microns of prostate biopsy core tissue is available (40 microns preferable), and
- Previous biopsy histology does not include a prior diagnosis of prostate cancer or cellular atypia suspicious for cancer (but may include the presence of high-grade prostatic intraepithelial neoplasia (HGPIN), proliferative inflammatory atrophy (PIA), or glandular inflammation), and
- Member is not being managed by active surveillance for low stage prostate cancer, and
- Tissue was extracted using standard patterned biopsy core extraction (and not transurethral resection of the prostate (TURP)), and
- Member has not been previously tested by ConfirmMDx from the same biopsy samples or similar molecular test

Decipher Biopsy Prostate Cancer Classifier Assay

Palmetto GBA a Medicare Administrative Contractor (MAC) that assesses molecular diagnostic technologies and establishes the coverage policy for Medicare beneficiaries has determined that **Decipher Biopsy Prostate Cancer Classifier Assay** is covered for Men with Favorable Intermediate Risk Disease and with Unfavorable Intermediate Risk Disease when the following criteria are met:

A. Favorable Intermediate Risk Disease Criteria:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and favorable intermediate risk disease defined as:
 - Gleason Grade Group 2 (Gleason Sum 3+4=7); **and**
 - Estimated life expectancy of greater than or equal to 10 years, **and**
- Member is a candidate for and is considering conservative management and yet would be eligible for definitive therapy (radical prostatectomy, radiation or brachytherapy), **and**
- Result will be used to determine treatment between definitive therapy and conservative management, **and**
- Member has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
- Member is monitored for disease progression according to established standard of care

B. Unfavorable Intermediate Risk Disease Criteria:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and unfavorable risk disease defined as:
 - Gleason score 3+4=7 / grade group 2 or Gleason score 4+3=7 / grade group 3, **or**
 - T2b to T2c, **or**
 - PSA 10-20 ng/mL, **and**
- Estimated life expectancy of greater than or equal to 10 years, **and**
- Member is a candidate for definitive therapy (RP +/- PLND, EBRT + ADT, or EBRT + brachytherapy +/- ADT), **and**
- Result will be used to determine treatment between definitive therapy modality, **and**
- Member has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
- Member is monitored for disease progression according to established standard of care

Prolaris, ProMark, OncoType Dx

Gene expression prognostic assay (eg, **Prolaris, ProMark, OncoType Dx**) is covered for members to help determine which members with early stage, needle biopsy proven prostate cancer can be conservatively managed rather than treated with definitive surgery or radiation therapy.

Palmetto GBA a Medicare Administrative Contractor (MAC) that assesses molecular diagnostic technologies and establishes the coverage policy for Medicare beneficiaries has determined that **Prolaris** testing will be considered for coverage when the following criteria are met:

1. Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**

2. Formalin fixed paraffin-embedded (FFPE) prostate biopsy specimen with at least 0.5 mm of cancer length, **and**
3. Member Stage as defined by the one of the following:
 - Very Low Risk Disease (T1c AND Gleason Score \leq 6 AND PSA \leq 10 ng/mL AND $<$ 3 prostate cores with tumor AND \leq 50% cancer in any core AND PSA density of $<$ 0.15 ng/mL/g) **OR**
 - Low Risk Disease (T1-T2a AND Gleason Score \leq 6 AND PSA \leq 10 ng/mL), and
4. Member has an estimated life expectancy of greater than or equal to 10 years, **and**
5. Member is a candidate for and is considering conservative therapy and yet would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), **and**
6. Result will be used to determine treatment between definitive therapy and conservative management, **and**
7. Member has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
8. Test is ordered by a physician certified in the Myriad Prolaris™ Certification and Training Registry (CTR), **and**
9. Member is monitored for disease progression according to established standard of care, **and**
10. Physician must report the development of metastasis or prostate cancer deaths in members not treated definitively who were deemed low risk by the assay.

OncoType DX AR-V7

Palmetto GBA a Medicare Administrative Contractor (MAC) that assesses molecular diagnostic technologies and establishes the coverage policy for Medicare beneficiaries has determined that **OncoType DX AR-V7** assay is covered when the following criteria are met:

1. The member is diagnosed with progressive mCRPC as defined by the Prostate Cancer Working Group 2 guidelines (a minimum of 2 rising prostate-specific antigen (PSA) levels 1 or more weeks apart, new lesions by bone scintigraphy, and/or new or enlarging soft tissue lesions by computed tomography or magnetic resonance imaging; and
2. The member has experienced failure on one androgen receptor signaling inhibitor (ARSi), (e.g., Enzalutamide (Xtandi), Apalutamide (Erleada), or Abiraterone (Zytiga).; and
3. The member is considered to be appropriate for treatment by their treating physician for the alternative ARSi as a single agent; and
4. Circulating tumor cells with nuclear expression of AR-V7 protein will be assessed prior to initiation of therapy

4Kscore

Palmetto GBA a Medicare Administrative Contractor (MAC) that assesses molecular diagnostic technologies and establishes the coverage policy for Medicare beneficiaries has determined that **4Kscore** testing will be considered for coverage when the following criteria are met:

- C. The member is 45 years of age and older, prior to an initial biopsy or following a negative biopsy, who has a confirmed moderately elevated PSA defined as greater than 3 and less than 10 ng/mL; **or**
- D. The member is 75 years of age and older, prior to an initial biopsy or following a negative biopsy, who has a confirmed moderately elevated PSA defined as greater than or equal to 4 and less than 10 ng/mL

and **BOTH** of the following are present:

3. No other relative indication for prostate biopsy including **ANY** of the following: (this may not be an all inclusive list):
 - DRE suspicious for cancer should be encouraged to undergo biopsy
 - Persistent and significant increase in PSA should be encouraged to undergo biopsy
 - Positive multiparametric magnetic resonance imaging (MRI) (if done)
 - Other major risk factor for prostate cancer including: (this may not be an all inclusive list)
 - Ethnicity at higher risk for prostate cancer
 - First-degree relative with prostate cancer
 - High-penetrance prostate cancer risk gene(s) per the National Comprehensive Cancer Network (NCCN) (if known)
4. No other relative contraindication for prostate biopsy including **ANY** of the following:
 - Less than a 10 year life expectancy
 - Benign disease not ruled out.

MEDICAID BUSINESS SEGMENT:

PA Dept. of Human Services has determined gene expression prognostic assay Prolaris is considered to be experimental/Investigational and therefore **NOT COVERED**.

PA Dept. of Human Services has determined PCA/CLK3 is considered to be experimental/Investigational and therefore **NOT COVERED**.

PA Dept. of Human Services has determined Oncotype DX Prostate Cancer Assay is considered to be experimental/Investigational and therefore **NOT COVERED**.

PA Dept. of Human Services has determined mRNA, microarray gene expression profiling of 22 content genes {Decipher} is considered to be experimental/Investigational and therefore **NOT COVERED**.

EXCLUSIONS:

Unless coverage is mandated, the Plan considers Promark™ **experimental, investigational, and unproven** for all indications including, but not limited to, the aid in predicting prostate cancer aggressiveness. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

Unless coverage is mandated, the Plan considers SelectMDx liquid biopsy testing **experimental, investigational, and unproven** for all indications including, but not limited to, aid in predicting the need for prostate biopsy or determining cancer risk stratification. There is currently insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes.

The Geisinger Technology Assessment Committee determined that at the present time, there is insufficient evidence in the peer-reviewed, published medical literature to support the use of PCA3 assay to determine the need for repeat biopsy in members who have had a previous negative prostate biopsy. Unless mandated by state or federal regulation, this testing is currently considered to be **experimental, investigational or unproven**, and therefore **NOT COVERED**.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

CODING ASSOCIATED WITH: Gene-based Testing and/or Protein Biomarkers for Diagnosis and Management of Prostate Cancer

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.

- 81313 PCA3 (prostate cancer antigen 3/ kallikrein-related peptidase 3) {Progenisa}
- 81479 Unlisted procedure
- 81539 Oncology (high grade prostate cancer), biochemical assay of four proteins (total PSA, free PSA, intact PSA and kallikrein-2) utilizing plasma or serum, prognostic algorithm reported as a probability score {4Kscore}
- 81541 Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score {Prolaris}
- 81542 Oncology (prostate), mRNA , microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score {Decipher®, Decipher® Prostate Cancer Assay or Decipher® Prostate Cancer Classifier}
- 81551 Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy [Confirm MDx]
- 88387 Macroscopic examination, dissection, and preparation of tissue for non-microscopic analytical studies (e.g., nucleic acid-based molecular studies); each tissue preparation (e.g., a single lymph node)

- 88363 Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)
- 0047U Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score {OncoType Dx Prostate}

Current Procedural Terminology (CPT®) © American Medical Association: Chicago, IL

LINE OF BUSINESS:

Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

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This policy will be revised as necessary and reviewed no less than annually.

Devised: 3/13

Revised: 2/15 (add Medicare & Medicaid coverage), 2/18 (title change, added clinical information); 8/18 (added exclusion for Medicaid) 8/19 (add coverage); 1/20 (add Decipher coverage; 4Kscore coverage for Medicare); 2/21 (added Medicaid Exclusions); 1/22 (add SelectMDx and 4K for Commercial)

Reviewed: 3/14, 2/16, 2/17,

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

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