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<b>Medical Benefit</b>		<b>Effective Date:</b> 10/01/17	<b>Next Review Date:</b> 05/18
<b>Preauthorization</b>	No	<b>Review Dates:</b> 09/09, 09/10, 07/11, 07/12, 05/13, 05/14, 05/15, 05/16, 05/17	

***This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.***

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>For whom an initial prostate biopsy or for whom a rebiopsy is being considered</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Genetic and protein prostate biomarker testing</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Standard clinical examination including measurement of percent free prostate-specific antigen</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Disease-specific survival</li> <li>Test accuracy</li> <li>Test validity</li> <li>Other test performance measures</li> <li>Resource utilization</li> <li>Hospitalizations</li> <li>Quality of life</li> <li>Treatment-related mortality</li> <li>Treatment-related morbidity</li> </ul>

### Description

Various genetic and protein biomarkers are associated with prostate cancer. These tests have the potential to improve the accuracy of differentiating which men should undergo prostate biopsy or rebiopsy after a prior negative biopsy. This protocol will address these types of tests for cancer risk assessment.

### Summary of Evidence

For individuals for whom an initial prostate biopsy or a rebiopsy is being considered who receive genetic and protein biomarker testing, the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, resource utilization, hospitalizations, quality of life, and treatment-related mortality and morbidity. The evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. In general, performance of biomarker testing for predicting biopsy compared with clinical examination, including the ratio of free or unbound prostate-specific antigen (PSA) to total PSA, is lacking. However, procedures for referrals for biopsy based on clinical examination vary, making it difficult to quantify performance characteristics for this comparator. There is considerable variability in biopsy referral practices based on clinical examination alone and many biomarker tests do not have standardized cutoffs to recommend biopsy.

Therefore, having prospective, comparative information on how test results are expected to be used or actually being used in practice and the associated effects on outcomes will be needed to determine if the tests improve net health outcomes. Many of the test validation populations have included men with a positive digital rectal exam, prostate-specific antigen (PSA) level outside of the gray zone, or older men for whom the information for test results are less likely to be informative. African Americans have a high burden of morbidity and mortality, but have not been well represented in these study populations. It is unclear how to monitor men with low biomarker risk scores who continue to have symptoms or high or rising PSA levels. Comparative studies of the many biomarkers are lacking and it is unclear how to use the tests in practice, particularly when test results are contradictory. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Policy

The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered **investigational**:

- Kallikrein markers (e.g., 4Kscore™ Test)
- Metabolomic profiles (e.g., Prostarix™)
- PCA3 testing
- TMPRSS fusion genes
- Candidate gene panels
- Mitochondrial DNA mutation testing (e.g., Prostate Core Mitomics Test™)
- Gene hypermethylation testing (e.g., ConfirmMDx®)
- Prostate Health Index (phi).

Single nucleotide polymorphism (SNPs) testing for cancer risk assessment of prostate cancer is considered **investigational**.

### Policy Guidelines

#### *Genetic Counseling*

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Medicare Advantage

#### *PCA3*

For Medicare Advantage PCA3 testing is considered **medically necessary** only when all biopsies in previous

encounter(s) are negative for prostatic cancer, the subsequent prostate specific antigen (PSA) is rising, and when the patient or physician wants to avoid repeat biopsy (“watchful waiting”).

When the physician plans to biopsy the prostate, a PCA3 test is considered **not medically necessary**.

All other indications for PCA3 are considered **not medically necessary**.

#### *ConfirmMDx*

For Medicare Advantage the ConfirmMDx epigenetic molecular assay is considered **medically necessary** under the following conditions:

1. 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**
2. The previous negative prostate biopsy must have collected a minimum of eight 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**
3. Minimum tissue volume criteria of 20 microns of prostate biopsy core tissue is available (40 microns preferable), **and**
4. 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**
5. Patient is not being managed by active surveillance for low stage prostate cancer, **and**
6. Tissue was extracted using standard patterned biopsy core extraction (and not transurethral resection of the prostate (TURP)), **and**
7. Patient has not been previously tested by ConfirmMDx from the same biopsy samples or similar molecular test, **and**
8. Testing has been ordered by a physician who is certified in the MoDx approved ConfirmMDx Certification and Training Registry (CTR) program\*.

#### **Medicare Advantage Policy Guidelines**

\*Because of the complicated nature of management decisions utilizing the ConfirmMDX assay and the potential for missing early prostate cancer, testing must be furnished only by physicians who are enrolled in a MoDx approved CTR program. Healthcare providers who order ConfirmMDX must be registered and certified in the ConfirmMDX CTR program. Coverage for ConfirmMDX testing is available only through these providers.

The ConfirmMDX epigenetic molecular assay may also be available through the PASCUAL clinical trial. Participation in the PASCUAL trial is not a prerequisite to the limited coverage.

#### **Background**

##### *Disease Description and Epidemiology*

Prostate cancer is the second most common cancer in men, with a predicted 181,000 incidence cases and 26,100 deaths expected in United States in 2016.<sup>1</sup>

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. Early localized disease can usually be cured with surgery and radiotherapy, although active surveillance may be adopted in men whose cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In patients with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. The lifetime risk of being diagnosed with prostate cancer for men in the United States is approximately 16%, but the risk of dying of prostate cancer is 3%.<sup>2</sup> African-American men have the highest prostate cancer risk in the United States; the incidence of prostate cancer is about 60% higher and the mortality rate is more than two to three times greater than that of white men.<sup>3</sup> Autopsy results have suggested that about 30% of men age 55 and 60% of men age 80 who die of other causes have incidental prostate cancer,<sup>4</sup> indicating that many cases of cancer are unlikely to pose a threat during a man's life expectancy.

The most widely used grading scheme for prostate cancer is the Gleason system.<sup>5</sup> It is an architectural grading system ranging from 1 (well differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 2 to 5 is regarded as normal prostate tissue; 6 is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. Ten-year survival rates stratified by Gleason score have been estimated from the Surveillance, Epidemiology, and End Results registry to be about 98% for scores 2 through 6, 92% for a score of 7 with primary pattern 3 and secondary pattern 4 (3+4), 77% for a score of 7 (4+3), and 70% for scores between 8 and 10.<sup>6</sup>

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for use of these molecular markers to improve selection of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

#### *Clinical Context and Test Purpose*

The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of men who should undergo biopsy or repeat biopsy. Conventional decision-making tools for identifying men for prostate biopsy include digital rectal exam (DRE), serum prostate-specific antigen (PSA), and patient risk factors such as age, race, and family history of prostate cancer.

DRE has relatively low interrater agreement among urologists, with estimated sensitivity, specificity, and positive predictive value (PPV) for diagnosis of prostate cancer of 59%, 94% and 28%, respectively.<sup>7</sup> DRE might have a higher PPV in the setting of elevated PSA.<sup>8</sup>

The risk of prostate cancer increases with increasing PSA levels; an estimated 15% of men with a PSA level of 4 ng/mL or less and normal DRE, 30% to 35% of men with a PSA level between 4 and 10 ng/mL, and more than 67% of men with a PSA level greater than 10 ng/mL will have biopsy-detectable prostate cancer.<sup>9,10</sup> Use of PSA levels in screening has improved detection of prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and Goteborg prostate cancer screening trials demonstrated that biennial PSA screening reduces the risk of being diagnosed with metastatic prostate cancer.<sup>11-15</sup>

However, elevated PSA levels are not specific to prostate cancer; levels can be elevated due to infection, inflammation, trauma, or ejaculation. In addition, there are no clear cutoffs for cancer positivity with PSA. Using a common PSA level cutoff of 4.0 ng/mL, the American Cancer Society (ACS) systematically reviewed the literature and calculated pooled estimates of elevated PSA sensitivity of 21% for detecting any prostate cancer and 5% for detecting high-grade cancers with estimated specificity of 91%.<sup>16</sup>

PSA screening in the general population is controversial. The U.S. Preventive Services Task Force recommended against PSA-based screening (D recommendation) in 2012 while guidelines published by ACS and the American Urological Association (AUA) endorsed consideration of PSA screening based on age, other risk factors, and estimated life expectancy.<sup>16-18</sup> The utility of PSA screening depends on whether screening can lead to management

changes that improve net health outcome. Results from the National Institutes for Health-supported Prostate Testing for Cancer and Treatment (Protect) trial demonstrated no difference in prostate cancer mortality rates between the treatment strategies of active monitoring, radical prostatectomy, and external-beam radiotherapy in clinically localized prostate cancer that is detected by PSA testing.<sup>19</sup>

These existing screening tools lead to unnecessary prostate biopsies because of their lack of specificity and inability to discriminate low- from high-risk prostate cancer. More than one million prostate biopsies are performed annually in the United States with a resulting cancer diagnosis in 20% to 30%. About one-third of men who undergo prostate biopsy experience transient pain, fever, bleeding, and urinary difficulties. Serious biopsy risks (e.g., bleeding or infection requiring hospitalization) are rare, with estimated rates ranging from less than 1% to 4%.<sup>20, 21</sup>

Given the risk, discomfort, and burden of biopsy and the low yield for diagnosis, there is a need for noninvasive tests that distinguish potentially aggressive tumors that should be referred for biopsy from clinically insignificant localized tumors that do not need biopsy or other prostatic conditions with the goal of avoiding low-yield biopsy. The following PICOTS were used to select literature that provides evidence relevant to this review.

### Patients

The relevant populations are men for whom an initial prostate biopsy is being considered because of clinical symptoms (e.g., difficulty with urination, elevated PSA) or men for whom a rebiopsy is being considered because the results of an initial prostate biopsy were negative or equivocal and other clinical symptoms remain suspicious.

The population for which these tests would potentially be most informative is men in the indeterminate or “gray zone” range of PSA on repeat testing with unsuspecting DRE findings. Repeat testing of PSA is important because results initially reported to be between 4 and 10 ng/mL are frequently normal.<sup>22</sup> The gray zone for PSA levels is usually between 3 or 4 and 10 ng/mL, but PSA levels varies with age. Age-adjusted normal PSA ranges have been proposed but not standardized or validated.

Screening of men with a life expectancy of less than 10 years is unlikely to be useful because most prostate cancer progresses slowly. However, the age range for which screening is most useful is controversial. The ERSPC and Goteborg trials observed benefits of screening only in men up to about 70 years old.

### Interventions

For assessing future prostate cancer risk, numerous studies have demonstrated the association between many genetic and protein biomarker tests and prostate cancer. Commercially available tests include those described in Table 1.

Table 1. Commercially Available Tests to Determine Candidate for Prostate Biopsy or Repeat Biopsy

Test	Manufacturer	Description
4Kscore <sup>®</sup>	OPKO lab	Blood test that measures four prostate-specific kallikreins, which are combine into an algorithm to produce a score
Prostarix <sup>™</sup>	Metabolon/Bostwick Laboratories	Urine test that measures several metabolites, which are combined with an algorithm to produce a score
Progenesa <sup>®</sup>	<ul style="list-style-type: none"> <li>Hologic Gen-Probe</li> <li>Many labs offer <i>PCA3</i> tests (e.g., ARUP Laboratories, Mayo Medical laboratories, and LabCorp)</li> </ul>	Urine test that measure <i>PCA3</i> mRNA
ConfirmMDx <sup>®</sup>	MDxHealth	Measure hypemethylation of three genes in tissue sample
Prostate Health	Beckman coulter	Blood test that combines several components of PSA

Test	Manufacturer	Description
Index™ (phi)		with an algorithm to produce a score
Prostate Core Mitomics Test™ (PCMT)	Mitomics (formerly Genesis Genomics)	Measures deletions in mitochondrial DNA by polymerase chain reaction in tissue sample

PSA: prostate specific antigen

In addition to commercially available tests, single-nucleotide polymorphism testing as part of genome-scanning tests for prostate cancer risk assessment are offered by a variety of laboratories, such as Navigenics (now Life Technologies), LabCorp (23andme), and ARUP Laboratories (deCODE), as laboratory-developed tests.

### Comparators

Standard clinical examination for determining who goes to biopsy might include DRE, review of history of PSA values, along with consideration of risk factors such as age, race, and family history. The ratio of free or unbound PSA to total PSA (%fPSA) is lower in men who have prostate cancer than in those who do not. A %fPSA cutoff of 25% has been shown to have a sensitivity and specificity of 95% and 20%, respectively, for a group of men with total PSA values between 4.0 and 10.0 ng/mL.<sup>23</sup>

The best way to combine all of the risk information to determine who should go to biopsy is not standardized. Risk algorithms have been developed that incorporate clinical risk factors into a risk score or probability. Two examples are the Prostate Cancer Prevention Trial (PCPT) predictive model<sup>24</sup> and the Rotterdam Prostate Cancer risk calculator (also known as the European Research Screening Prostate Cancer Risk Calculator 4 [ERSPC-RC]).<sup>25</sup> The AUA and the Society of Abdominal Radiology recently recommended that high-quality prostate magnetic resonance imaging, if available, should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy.<sup>26</sup>

### Outcomes

Outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, resource utilization, hospitalizations, quality of life, and treatment-related mortality and morbidity.

The beneficial outcome of the test is to avoid a biopsy that would be negative for prostate cancer. A harmful outcome is failure to undergo a biopsy that would be positive for prostate cancer, especially when disease is advanced or aggressive. Thus the relevant measures of clinical validity are the sensitivity and negative predictive value. The appropriate reference standard is biopsy. Prostate biopsies are not perfect for diagnosis. Biopsies can miss cancers and repeat biopsies are sometimes needed to confirm diagnosis. Detection rates vary by method used for biopsy and patient characteristics, with published estimates between 14% and 22% for the initial biopsy, 10% and 28% for a second biopsy, and 5% and 10% for a third biopsy.<sup>27, 28</sup>

### Time

The timeframe of interest for calculating performance characteristics is time to biopsy result. Men who forgo biopsy based on test results could miss or delay diagnosis of cancer. Longer follow-up would be necessary to determine effects on overall survival.

### Setting

Initial screening using PSA levels and DRE may be performed in primary care with referral to specialty (urologist) care for suspicious findings and biopsy. Clinical practice regarding screening methods and frequency vary widely.

## Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore®), Metabolon (Prostarix™), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (ConfirMDx), and Innovative Diagnostics (phi™), are CLIA-certified. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In February 2012, the Progenesa® PCA3 Assay (Gen-Probe; now Hologic) was approved by FDA through premarket approval process. According to the company's press release, this assay is "indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of Progenesa PCA3 assay results." FDA product code: OYM.

In June 2012, pro-PSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter) was approved by FDA through the premarket approval process. The phi test is indicated as an aid in distinguishing prostate cancer from benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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125. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): MOLECULAR Pathology Procedures (L35000), Revision Effective Date for services performed on or after 02/1/2017.
126. Noridian Healthcare Solutions, LLC, (Jurisdiction - California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) Local Coverage Determination (LCD): MoIDX-CDD: CONFIRMMDX Epigenetic Molecular Assay (L36327), Revision Effective Date for services performed on or after 10/01/2016.