Clinical Policy Title: Genetic tests for prostate cancer prognosis

Clinical Policy Number: 13.01.01

Effective Date: January 1, 2015
Initial Review Date: July 16, 2014
Most Recent Review Date: August 17, 2016
Next Review Date: August 2017

Policy contains:
- PROGENSA® urine test.
- PCA3 test.
- Tests for gene fusion or polymorphism.
- Newly diagnosed or active surveillance patients.

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the use of genetic testing for prostate cancer prognosis to be investigational and, therefore, not medically necessary.

Limitations:

Note: The following CPT/HCPCS codes are not listed in the Pennsylvania Medicaid fee schedule:

81479 - TMPPRSS fusion gene testing

S3721 - Cancer antigen 3 (PCA3) testing (Not Covered by Medicare)

Alternative covered services:

Standard diagnostic and radiographic tests for prostate cancer (e.g., prostate specific antigen [PSA], radionuclide bone scan).

Background
Genetic testing or gene expression testing/classification includes a variety of laboratory tests (analysis of deoxyribonucleic acid [DNA], ribonucleic acid [RNA], genes or gene products) for the purposes of diagnosing disease, assisting in treatment decisions (in the case of prostate cancer, decisions about immediate or more aggressive versus delayed treatment), predicting future disease, identifying carriers of disease or prenatal testing.

The PROGENSA® PCA3 assay (also known as the Mi Prostate Score or miPS) is an in vitro nucleic acid amplification test to measure the concentration of prostate cancer gene 3 (PCA 3), PSA and the relative concentrations of respective RNA molecules in urine collected after a digital rectal exam (DRE). It was approved for marketing by the U.S. Food and Drug Administration (FDA) in 2012, with indication for use “in conjunction with other information to aid the decision for repeat biopsy in men 50 years 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 current standard of care, before consideration of this test’s results. A PCA3 score < 25 is associated with a decreased likelihood of a positive biopsy. Prostatic biopsy is required for diagnosis of cancer.”

Promotional materials advocate the test as an adjunct to and improvement over standard PSA screening for its ability to identify men with high-risk tumors and thus avoid unnecessary biopsies and the other harms of over-diagnosis by PSA discussed below.

Prostate cancer is the most common noncutaneous malignancy and the second-leading cancer cause of death in men. Ninety percent of men with prostate cancer are over age 60, diagnosed with a PSA blood test and have clinically localized disease. Common treatments for clinically localized prostate cancer include watchful waiting and surgery to remove the prostate gland (radical prostatectomy), external beam radiation therapy and interstitial radiation therapy.

Prostate cancer is a clinically heterogeneous disease. A substantial proportion of prostate cancer cases detected with current screening methods will never cause symptoms during the patients’ lifetimes. Modeling studies based on U.S. incidence data suggest over-diagnosis rates ranging from 29 percent to 44 percent of all prostate cancer cases detected by PSA screening. Because patients with “pseudo-disease” receive no benefit from, and may be harmed by, prostate cancer screening and treatment, prostate cancer detection in this population constitutes an important health financing burden. Review bodies have consistently found insufficient evidence that screening for prostate cancer improves health outcomes, including mortality, while noting evidence on the harms of the screening process and the often-benign natural history of prostate cancer detected with screening.

Prostate cancer screening is problematic because it attempts to mitigate a disease of which we have a poor understanding by using a test not well suited to the job, with rates of over-diagnosis estimated at 20 percent to 50 percent for a disease with a current annual incidence > 186,000 in the United States alone. Side effects of treatment can be considerable and may include lasting effects on urinary, bowel, sexual and vitality functions. Unfortunately, even patients with clear evidence of indolent disease, who are candidates for surveillance, suffer from cancer diagnosis. Indeed, the most common reason patients stop surveillance and have active treatment is anxiety, not disease progression.

The Gleason score is a system of grading prostate cancer based on its microscopic appearance. It indicates the sum of predominant histological pattern (graded 1 to 5) and the next most common pattern. Gleason scores range from 2 to 10, indicating likelihood that a tumor will spread. The higher the score is, the higher the likelihood of spread. Needle biopsy specimens (versus those from radical
prostatectomy) provide insufficient tissue for complete Gleason scoring and cannot be scored lower than 6 (3 + 3).

Gleason, PSA levels and tumor staging together comprise standard risk stratification:

<table>
<thead>
<tr>
<th>Risk</th>
<th>PSA (ng/ml)</th>
<th>Gleason</th>
<th>Tumor stage</th>
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<tbody>
<tr>
<td>Low</td>
<td>&lt; 10</td>
<td>&lt; 6</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 – 20</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 20</td>
<td>8 – 10</td>
<td>3 – 4</td>
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</tbody>
</table>

**Searches**

Keystone First searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on August 3, 2016. Search terms were “prostate cancer,” “risk stratification,” and “genetic tests.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Diagnostic testing for prostate cancer has been the subject of much methodological discussion, summarized by Muir Gray (1997) and Sackett (1991). Briefly, evaluation of diagnostic technology entails five levels (Banta and Luce, 1993):

1. Technical evaluation — The technical output gives accurate information concerning the structure of the body part imaged.
2. Diagnostic accuracy — This output concerns information that potentially improves the clinician’s ability to diagnose disease and assess the patient’s prognosis.
3. Diagnostic impact — The information can alter plans for additional diagnostic tests.
4. Therapeutic impact — The information can lead to changes in therapeutic plans for patients.
5. Health impact — The end result may be improved patient outcome.

- FDA reviewers are satisfied that technical and diagnostic accuracy levels of evaluation (outlined above) for the PROGENSA test have been adequately documented for marketing approval (2012).
- CMS has not addressed the test in any coverage decision.
Available reviews focus on pre-clinical (laboratory) or observational research, which is still in the process of identifying optimal genetic or molecular markers to identify those men receiving active surveillance who are likely to die from, rather than with, their cancers; in other words, risk assessment for prostate cancer remains at the hypothesis-generating level (cross-sectional associations of marker concentrations with tumor volume or other intermediate/surrogate endpoints) rather than testing level (trials or cohort studies following tested patients forward in time to assess outcomes).

Alternate approaches such as nomograms or refinements to imaging or to PSA testing are also under development.

Research confirming that any currently available tests, or those under development, actually impact therapeutic decisions or health outcomes has yet to be published or addressed in systematic reviews.

Policy updates:

Liu (2016) reported that somatically acquired aberrations in prostate cancer are highlighted by DNA copy number alterations and TMPRSS2-ERG fusion derived from complex rearrangements, numerous single nucleotide variations or mutations, tremendous heterogeneity, and continuously punctuated evolution. Genome-wide copy number alterations, gain in primary tumors, loss/mutation and amplification/mutation in advanced metastatic prostate cancer are consistently associated with worse cancer prognosis. With this recently gained knowledge, it is now an opportune time to develop DNA-based tests that provide more accurate patient stratification for prediction of clinical outcome, which will ultimately lead to more personalized cancer care than is possible at present.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content</th>
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</thead>
<tbody>
<tr>
<td>Liu (2016)</td>
<td>DNA alterations in the tumor genome and their associations with clinical</td>
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<tr>
<td></td>
<td>outcome in prostate cancer.</td>
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<tr>
<td></td>
<td>Key points:</td>
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<tr>
<td></td>
<td>• Somaically acquired aberrations in prostate cancer are highlighted by</td>
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<td>Bjurlin (2014)</td>
<td>Optimization of prostate biopsy; the role of magnetic resonance imaging targetted biopsy in detection, localization, and risk assessment.</td>
</tr>
<tr>
<td></td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Multiparametric MRI for risk assessment.</td>
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<tr>
<td></td>
<td>• Relevant studies of unspecified design – October 2013.</td>
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<tr>
<td></td>
<td>• Anatomical T2-weighted MRI + at least two functional imaging techniques improved detection sensitivity up to 80% in peripheral zone and 91% in transition zone.</td>
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<tr>
<td></td>
<td>• Potential for reducing sampling error but clinical application needs further investigation.</td>
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<tr>
<td>Yao (2014)</td>
<td>Evaluation of the TMPRSS2:ERG fusion for</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>• TMPRSS2: ERG fusion.</td>
</tr>
<tr>
<td></td>
<td>• Diagnostic accuracy studies – July 2013.</td>
</tr>
<tr>
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</table>
| the detection of prostate cancer: a systematic review and meta-analysis. | • Presence of fusion in body fluids, needle biopsy or surgical specimens.  
• Thirty-two studies.  
• Pooled Se, 49.0%; Sp, 90.2%.  
• Fusion not suitable as screening test but may have potential for confirming diagnosis. |
| Andrés (2013) | **Key points:**  
• DNA methylation in urological cancer.  
• Potential for early diagnosis and screening but further research needed to confirm clinical applications. |
| The study of DNA methylation in urological cancer: present and future. | **Key points:**  
• PCA3 testing for diagnosis and management.  
• Evidence insufficient for all three key questions: poor quality of all studies. |
| Bradley (AHRQ; 2013) | **Key points:**  
• Methylation markers for prostate cancer prognosis.  
• Hunan studies examining association between markers and prognosis.  
• 20 (Ns from 35 to 605).  
• Evidence inconclusive. |
| PCA3 testing for the diagnosis and management of prostate cancer. | **Key points:**  
• Gene polymorphisms and prostate cancer risk.  
• Case-control or nested case-control – March 2013.  
• Thirty-four studies, 910,267 cases, 11,489 controls: no evidence for an association. |
| Chao (2013) | **Key points:**  
• Steroid 5-alpha-reductase type 2 polymorphisms and sporadic prostate cancer risk: insufficient evidence. |
| Methylation markers for prostate cancer prognosis. | **Key points:**  
• Detection of prostate cancer in urine.  
• Insufficient evidence for early detection of aggressive subsets. |
| Guo (2013) | **Key points:**  
• Multi-gene panes in prostate cancer risk assessment.  
• Studies confirming analytic validity/accuracy of commercially available tests – October 2011.  
• Fourteen studies primarily relevant to key question 2 (clinical validity of SNP-based panels for risk assessment but also permitted extrapolation to question 1(analytic validity); no direct assessments of analytic validity available; and no studies for clinical utility.  
• All studies had at least moderate risk of bias. |
| Little (AHRQ; 2012) | **Key points:**  
• Prostinoegen genetic variants and prostate cancer risk or aggressiveness. |
| Multigene panels in prostate cancer risk assessment. | **Key points:**  
• Prostinoegen genetic variants and prostate cancer risk or aggressiveness. |
| Health care technology and its assessment: an | **Key points:**  
• Prostinoegen genetic variants and prostate cancer risk or aggressiveness. |
Potential role among men of European ancestry but further research required.

### Glossary

**Nomogram** — A graphical calculating device commonly consisting of parallel vertical scales, corresponding to the number (n) of variables in an equation. When values for n-1 variables are known, a straightedge connecting them approximates the unknown value.

**Prostate-specific antigen (PSA)** — An enzyme (biochemical catalyst) produced by malignant and non-malignant prostate epithelial cells, making it prostate-specific but not prostate cancer-specific. It also increases from prostatitis and benign prostatic hyperplasia. PSA testing for early detection of prostate cancer was approved by the FDA in 1994 and widespread testing has played a significant role in the proportion of men diagnosed with early stage cancers; newly diagnosed cancers are organ-confined or localized in more than 70 – 80 percent of men. As noted above, PSA levels are strongly associated with risk and outcomes of prostate cancer treatment.

**Radical prostatectomy** — Surgical removal of the prostate.

**Sensitivity** — The proportion of people with the disease who have a positive test result. A sensitive test will rarely miss the disease, hence is used when there is an important penalty for missing a diagnosis, as in early localized and treatable cancers.

**Specificity** — The proportion of people without a disease who have a negative test result.

**Watchful waiting or active surveillance** — An approach to low-risk, localized prostate cancer involving regular PSA testing, digital rectal exam and prostate biopsy that avoids the adverse effects (erectile dysfunction, urinary leakage or incontinence) associated with the immediate treatment options and defers treatment until mandated by symptoms or objective signs of tumor progression.

### References

**Professional society guidelines/other:**


**Peer-reviewed references:**


Clinical trials:

Searched clinicaltrials.gov on August 3, 2016 using terms “genetic test,” “prostate cancer” and “prognosis” | Open Studies. 43 studies found, 1 relevant.


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes
Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm, prostate.</td>
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