Cigna Medical Coverage Policy

Subject: Gene-Based Testing for Prostate Cancer Screening, Detection and Disease Monitoring

Effective Date: 4/15/2014
Next Review Date: 4/15/2015
Coverage Policy Number: 0332

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Coverage Policy

Cigna does not cover gene-based testing for screening, detection and/or disease monitoring of prostate cancer because it is considered experimental, investigational or unproven. Testing includes, but is not limited to the following:

- PCA3 (e.g., PROGENSA PCA3®)
- Decipher®
- OncotypeDX® Prostate
- Prolaris®
- Kallikrein-related peptidase 2 (hK2)
- Single-nucleotide polymorphisms (SNPs)
- Candidate gene panels
- Gene hypermethylation/DNA methylation (e.g., ConfirmMDx™)
- TMPRSS2:ERG fusion genes (e.g., ProstaVysion®)

General Background

The expression and function of numerous genes have been shown to be altered in prostate cancer. Many of these genes are involved in cell cycle regulation, steroid hormone metabolism or regulation of gene expression. Analysis of changes in the levels of expression of large numbers of genes during prostate cancer progression has provided a better understanding of the basis of the disease, yielding new molecular markers with potential use in diagnosis and prognosis (Foley, et al., 2004).
Although serum prostate-specific antigen (PSA) measurement is regarded as the best conventional serum tumor marker available for prostate cancer, it has great limitations as well. Despite its adequate sensitivity, the use of PSA is limited by significant lack of specificity. Consequently, the clinical assessment of patients with an elevated PSA value will result in the performance of unnecessary prostatic biopsies in a substantial number of men. This can be explained by the fact that PSA is not specific for prostate cancer. One proposed approach to improve diagnostic accuracy of tests for prostate cancer and to reduce the number of biopsies is to identify prostate cancer-specific genes (Hessels, et al., 2003).

Prostate Cancer Gene 3 (PCA3)
One such gene is prostate cancer gene 3 (PCA3), which is also known by the symbol DD3, a prostate-specific gene that is highly overexpressed in prostate cancer tissue. Investigators pursued the analysis of urine obtained after digital rectal examination (DRE). Ribonucleic acid (RNA) was extracted from the samples and tested by reverse transcription-polymerase chain reaction (RT-PCR) assay for PCA3. PCA3 testing in clinical practice focuses on the detection of the PCA3 in urine samples following a digital rectal exam.

One proposal is to use the PCA3 assay in conjunction with serum PSA measurements and digital rectal examination (DRE) to assist in decision making regarding the need for biopsy in men undergoing evaluation for prostate cancer. A ratio of the PCA3 mRNA and PSA mRNA in the urine are calculated to provide a PCA score. It is proposed that the PCA score provides the expression of PCA3 corrected for the background of prostate cells present in the specimen. It is also thought that this measurement may serve to validate that the yield of prostate specific RNA is sufficient to generate a valid or informative test.

U.S. Food and Drug Administration (FDA)
February 2012, the PROGENSA PCA3© (Gen-Probe, San Diego, CA) assay received FDA Premarket Approval (PMA). The PMA notes that the progensa pca3 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 current standard of care, before consideration of progensa pca3 assay results. A pca3 score <25 is associated with a decreased likelihood of a positive biopsy. Prostatic biopsy is required for diagnosis of cancer.

The FDA approval includes a Black Box warning: The PROGENSA PCA3 Assay should not be used for men with atypical small acinar proliferation (ASAP) on their most recent biopsy. Men with ASAP on their most recent biopsy should be treated in accordance with current medical guidelines.

A warning is included in the FDA approval: The Clinical Study of the PROGENSA PCA3 assay only included men who were recommended for a repeat biopsy. Therefore, the performance of the PROGENSA PCA3 Assay has not been established in men for whom a repeat biopsy was not already recommended.

Literature Review—Prostate Cancer Gene 3 (PCA3)
The Agency for Healthcare Research and Quality (AHRQ) conducted a comparative effectiveness review for PCA3 testing for the diagnosis and management of prostate cancer, prepared by the Blue Cross and Blue Shield Technology Evaluation Center Evidence-based Practice Center (Bradley, et al., 2013). Inclusion criteria required PCA3 and at least one comparator to be measured in the same cohort in one of the three clinical settings: at-risk men considering initial biopsy; at-risk men considering repeat biopsy; and men with prostate cancer making treatment decisions based on risk categorization. Analyses were matched by comparing within study differences between PCA3 and a comparator. Modeling was used to smooth consensus ROC curves and to address issues relating to verification bias. Diagnostic accuracy studies were assessed for quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Strengths of evidence were judged high, moderate, low, or insufficient according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria and the AHRQ “Methods Guide for Medical Test Reviews.”

The review included 24 studies that provided data that could be used to address diagnostic accuracy and 13 studies that addressed decision-making based on risk stratification criteria. All studies were of poor quality. Comparison of PCA3 to total PSA (tPSA) had the most available studies (22) but was subject to spectrum, verification, and sampling biases. The report observed that:
• PCA3 is more discriminatory for detecting cancers (i.e., at any sensitivity, the specificity is higher, or at any specificity, the sensitivity is higher) than tPSA elevations.
• This finding appears to apply to both initial and repeat biopsies.
• PCA3 and tPSA are relatively independent predictors.
• The strength of evidence was low.
• For all other diagnostic accuracy comparisons, and all intermediate and long-term health outcomes, the strength of evidence was found to be insufficient.
• For treatment decision-making in men with positive biopsy, in all comparisons for intermediate and long-term health outcomes, the strength of evidence was found to be insufficient.

The report concluded that for diagnostic accuracy, there was a low strength of evidence that PCA3 had better diagnostic accuracy for positive biopsy results than tPSA elevations, but insufficient evidence that this led to improved intermediate or long-term health outcomes. For all other settings, comparators, and outcomes, there was insufficient evidence.

ECRI published an emerging technology evidence report regarding PCA3 assay for aiding repeat biopsy decision making for suspected prostate cancer (ECRI, 2013). Findings to the key questions include:

• Regarding the accuracy of the Progensa PCA3 assay for predicting which patients do not require repeat prostate biopsy:
  - Twelve studies reported the accuracy of the Progensa PCA3 assay for predicting prostate biopsy result. Three studies used the PCA3 score threshold (25) identified in the FDA-approved labeling for Progensa. These three studies reported that the specificity of the PCA3 assay ranges from 57.1% to 64% and the NPV ranges from 77.3% to 91%.
  - Other published studies determined specificity and NPV at threshold values ranging from 12 to 70.
  - A change in the PCA3 score threshold may change the PCA3 assay’s predictive accuracy.
• Regarding the accuracy of the Progensa PCA3 assay for predicting which patients do not require repeat prostate biopsy compared with the accuracy of any other repeat biopsy decision-making aid:
  - Due to limited data, a comparison of the accuracy of the Progensa PCA3 assay to the accuracy of other decision-making aids could not be performed. No comparative study used the PCA3 score threshold identified in the FDA-approved labeling for Progensa.
  - Only one study compared the accuracy of the PCA3 score for predicting prostate biopsy result to the accuracy of the free to total PSA ratio (f/t PSA). The results of that study showed PCA3 score >35 and f/t PSA ≤15% were significantly more specific than PCA3 score >20, f/t PSA ≤20%, and f/t PSA ≤25%, and PCA3 score >20, f/t PSA ≤20% and f/t PSA ≤25% had significantly greater NPV than PCA3 score >35 and f/t PSA ≤15%. Only one study compared the PCA3 assay to parametric magnetic resonance imaging (MRI). The investigators reported the specificity and NPV of the multiparametric MRI (86.6% and 86.6%) were greater than the PCA3 assay (66.6% and 62.5%) but did not report a statistical analysis of the comparison. The data provided by the investigators was insufficient to perform a statistical comparison.
• Regarding the use of the PCA3 assay added to standard practice (e.g., total PSA, DRE, patient characteristics) decrease the number of repeat prostate biopsies: No studies addressed this key question.
• Regarding PCA3 assay, compared with any other repeat biopsy decision making aid, lead to improved clinical outcomes (i.e., number of prostate biopsies, biopsy-related complications, patient satisfaction, quality of life, morbidity, mortality) in patients who have had at least one previous negative biopsy result and for whom another biopsy is recommended: No studies addressed this key question.

In the report, the ECRI Institute searches did not identify any ongoing trials of PCA3 assays (Progensa) for patients with prostate cancer.

Wu et al. (2012) reported on a retrospective study of 103 patients that that examined the utility of PCA3 in combination with other clinical data in predicting the risk of prostate cancer on repeat biopsy. PCA3, PSA, PSA density (PSAD), digital rectal examination (DRE) and transrectal ultrasound findings were obtained retrospectively. Of the 103 patients, 37 (31%) had prostate cancer on repeat biopsy. The sensitivity of PCA3 was 0.67 and the specificity was 0.64. There were limitations to this study including: the retrospective nature of these data may create bias; not all individuals receiving a PCA3 assay underwent repeat biopsy. In addition,
several other prostate cancer markers including percent free PSA, PSA velocity and PSAD of the transition zone have been suggested as highly sensitive and specific for prostate cancer—these values were unavailable in these data, but addition of these factors to the nomogram may have further improved its diagnostic accuracy. Further studies are needed for validation and to provide evidence of the clinical utility of PCA3 test. 

de la Taille et al. (2011) reported on a prospective, multicenter, observational study that evaluated the clinical utility of the PCA3 assay in guiding initial biopsy decisions. The study included 516 men with a serum total prostate specific antigen of 2.5–10 ng/ml scheduled for initial biopsy. The patients PCA3 scores were determined using the PROGENSA PCA3 assay and compared to biopsy outcome. The diagnostic accuracy of PCA3 was compared to total prostate specific antigen, prostate specific antigen density and %free prostate specific antigen. The performance of the PCA3 assay was evaluated for sensitivity and specificity by comparing the PCA3 score to biopsy outcome. The positive biopsy rate was 40%. An increasing PCA3 score corresponded with an increasing probability of a positive biopsy. The mean PCA3 score was higher in men with a positive as compared to a negative biopsy (69.6 vs 31.0, median 50 vs 18, p<0.0001). The PCA3 score was independent of age, total prostate specific antigen and prostate volume. The PCA3 score (cutoff of 35) had a sensitivity of 64% and specificity of 76%. The ROC analysis showed a significantly higher AUC for the PCA3 score vs total prostate specific antigen, prostate specific antigen density and %free prostate specific antigen. The PCA3 score was significantly higher in men with biopsy Gleason score 7 or greater vs less than 7, greater than 33% vs 33% or fewer positive cores and significant vs indolent prostate cancer. Inclusion of PCA3 in multivariable models increased their predictive accuracy by up to 5.5%. The authors concluded that the PROGENSA PCA3 assay may improve the prediction of initial biopsy outcome. While the PCA3 score appears to be more accurate for predicting biopsy outcomes, it is still unknown what the appropriate cutoff for PCA3 score and the utility of this test for biopsy decisions. It should be further studied whether the PCA3 score may also be indicative of prostate cancer aggressiveness and if it can aid in the selection of men who can be treated with active surveillance. Limitations of the study included that it was not non-randomized study, and not all the men had %free PSA measurements, which may have caused selection bias. Further investigations and prospective clinical trials are needed to assess the prognostic performance of the test and to determine the appropriate utility and cutoff for the PCA3 score. 

Auprich et al. (2011) reported on a systematic review that evaluated the current evidence regarding the biologic and analytic approach of urinary prostate cancer gene 3 (PCA3) in prostate cancer (PCa) detection, staging, and prognosis, and its therapeutic potential. The review included 47 PCA3 studies, including nine basic papers, 19 and seven reports on diagnostic and staging, respectively, and 12 studies on new diagnostic and therapeutic concepts of PCA3. The review noted that PCA3 improves the diagnostic accuracy of externally validated nomograms among men with an elevated PSA undergoing biopsy. The review indicated that PCA3 independently predicts low-volume disease and pathologically insignificant prostate cancer but is not associated with locally advanced disease and is limited in the prediction of aggressive cancer. The preliminary data demonstrates that combining PCA3 with other new biomarkers may further improve diagnostic and prognostic accuracy. 

Aubin et al. (2010) reported on a study that examined performance of PCA3 alone and in presence of other covariates as an indicator of prostate biopsy results in patients with previous negative biopsy and increased PSA levels. PCA3 scores were determined in 1,072 patients before the year two and year four biopsies from patients in the placebo arm of the REDUCE trial, a prostate cancer risk reduction study evaluating men with moderately increased serum PSA results and negative biopsy at baseline. PCA3 scores were associated with positive biopsy rate (p<0.0001) and correlated with biopsy Gleason score (p=0.0017). The multivariate logistic regression model yielded an area under curve (AUC) of 0.753 and exclusion of PCA3 from the model decreased AUC to 0.717 (p=0.0009). PCA3 at year two was a significant predictor of year four biopsy outcome (AUC 0.634; p=0.0002), while serum PSA and free PSA were not predictive (p=0.3281 and 0.6782 respectively). 

A study was conducted a study to evaluate the association between PCA3 and cancer significance by reviewing the relationship between urinary PCA3 levels and surveillance biopsy results in 294 men with prostate cancer in a surveillance cohort (Tosoian, et al., 2010). Patients with progression on biopsy (12.9%) had a mean PCA3 score similar to that of those without progression. After adjustment for age and date of diagnosis PCA3 was not significantly associated with progression on biopsy (p=0.15).
The Blue Cross Blue Shield Technology Evaluation Center (TEC) published a special report regarding the recent developments in prostate cancer genetics and genetic testing (TEC, 2009). In regards to PCA3 testing, the report notes that:

- Study results suggest that the PCA3 score provides incremental improvement over PSA measurement in discriminating patients with eventual benign biopsies from those with malignant biopsy results, and markedly improves upon serum PSA specificity.
- PCA3 score may also have value in identifying patients with less aggressive cancer who may only need surveillance.
- Results to date are preliminary. Interpretation of assay results has not been standardized (i.e., cutoff value). The clinical utility (i.e., that using the test will improve outcomes) studies of decision-making for initial biopsy, repeat biopsy or treatment have not been reported.
- Regarding the studies for tests in prostate cancer genetics, the report notes that the assays are in a developmental phase and currently without evidence of clinical utility.

The potential utility of the PCA3 assay in patients with elevated PSA levels and negative prostate biopsy findings was evaluated (Marks, et al., 2007). In 226 patients, repeat biopsy indicated 60 were positive for cancer and 166 were negative. A PCA3 score of 35 corresponded to the greatest degree of accuracy with a sensitivity of 58%, a specificity of 72%, and an odds ratio of 3.6. The risk of positive biopsy findings increased with an increasing PCA3 score. At PCA3 scores of less than five, 12% of the patients had positive biopsy findings. PCA3 scores of greater than 100 had a 50% probability of a positive biopsy. This study suggests that the PCA3 urine assay may assist in treatment decisions in patients with elevated PSA levels and negative prostate biopsy findings but needs to be validated with further well designed studies.

Several case studies and cohort studies have been conducted that examine PCA3 utilized in conjunction with PSA testing, generally with men who have an elevated PSA and who have been referred for biopsy (Ochiai, et al., 2011; Shappell, et al., 2008; Haese, et al., 2008; Deras, et al., 2008; Nakanishi, et al., 2008; Sokoll, et al., 2008; van Gils, et al., 2007; Marks, et al., 2007; Groskopf, et al., 2006; Fradet, et al., 2004; Tinzl, et al., 2004; Hessels, et al., 2003). These studies have demonstrated that there is a correlation between the urine PCA3 score and the probability of positive biopsy. In addition the PCA3 has been shown that the performance characteristics demonstrate stability across serum PSA levels and independence from prostate volume (Deras, et al., 2008).

Limitations of the PCA3 include the lack of an international standard for the urinary assay and all methods rely upon urine obtained immediately after an attentive DRE (Wang, et al., 2009). It is not clear if a suboptimal DRE or a small peripheral tumor producing a minimal of shed cells into the urine will result in a falsely negative PCA3 score. In addition, while a PCA3 score of ≥35 has been proposed as a preliminary positive cut-point; one study noted that 33.9% of the men with a PCA3 score ≥35 had prostate cancer on biopsy (Wang, et al., 2010).

The process of finding new biomarkers to replace or augment the existing best marker, PSA, requires standardized phases of evaluation and validation. To date, a number of different assays and thresholds have been used, raising questions of reproducibility and standardization (Wright et al., 2007). Preliminary studies of the PCA3 test indicate that the sensitivity is less than that of PSA, but the specificity appears to be better, in particular with patients who have had a negative biopsy (Vlaeminck-Guillem, et al., 2010). A review of 11 studies published regarding PCA3 test indicated that sensitivity for the test ranged from 54-82% which was less than PSA test and the specificity ranged from 66-89% which is considered better than the PSA test (Vlaeminck-Guillem, et al., 2010). The review also found that positive predictive value (48-75%) and negative predictive value (74-90%) for PCA3 test were better than seen with PSA.

The role of PCA3 in clinical practice has yet to be validated in well-designed clinical trials. Studies need to be conducted to confirm the preliminary findings, refine assay standardization, and define the most relevant patient population for application (Wang, et al., 2010).

**TMPRSS2:ERG Fusion Genes**

TMPRSS2 is an androgen-regulated transmembrane serine protease that is preferentially expressed in normal prostate tissue. In prostate cancer, it may be fused to an ETS family transcription factor (ERG, ETV1, or ETV4), which transforms transcription of target genes involved in cell growth, transformation, and apoptosis. The result
of gene fusion with an ETS transcription gene is that the androgen responsive promoter of TMPRSS2 positively dysregulates expression of the ETS gene, which may be indicative of a mechanism for neoplastic transformation. Fusion genes may be found in tissue or urine. It is proposed that assays for fusion genes may offer specific disease detection, and that fusion genes are associated with a greater likelihood of biochemical recurrence. However, accurate fusion gene detection is complex, assays have not been standardized, and once they are, larger studies will be needed to determine clinical utility (Blue Cross Blue Shield Technology Evaluation Center [TEC], 2009).

**ProstaVysion:** ProstaVysion (Bostwick Laboratories, Glen Allen, VA), a prognostic genetic panel for prostate cancer. A tissue-based panel, this test examines two mechanisms of prostate carcinogenesis: ERG gene fusion/translocation and the loss of the PTEN tumor suppressor gene. It is proposed that by examining these two markers that the test can provide a molecular analysis of prostate cancer aggressiveness and long-term patient prognosis.

Stephan et al. (2013) reported on a comparative assessment of 246 men that compared urinary PCA3, TMPRSS2:ERG gene fusion (T2:ERG), and the serum proprostate-specific antigen-based prostate health index (Phi) for predicting biopsy outcome. Prostate cancer (PCa) was diagnosed in 110 (45%) and there was no evidence of malignancy (NEM) in 136 (55%). A first set of biopsies was performed in 136 (55%) of all men, and 110 (45%) had ≥1 repeat biopsies. PCA3, Phi, and T2:ERG differed significantly between men with PCa and NEM, and these markers showed the largest areas under the ROC curve (AUCs) (0.74, 0.68, and 0.63, respectively). PCA3 had the largest AUC of all parameters; however, not statistically different from Phi. Phi showed somewhat lower specificities than PCA3 at 90% sensitivity. Combination of both markers enhanced diagnostic power with modest AUC gains of 0.01–0.04. Although PCA3 had the highest AUC in the repeat-biopsy cohort, the highest AUC for Phi was observed in DRE-negative patients with PSA. The authors concluded that PCA3 and Phi were superior to the other evaluated parameters but their combination gave only moderate enhancements in diagnostic accuracy for PCa at first or repeat prostate biopsy.

Evidence in the published peer-reviewed scientific literature regarding the clinical utility of TMPRSS2/ERG fusion genes, and these fusion genes in combination with other biomarkers is lacking.

**Kallikrein-related Peptidase 2 (hK2)**

Kallikrein-related peptidase 2 (HK2 or KLK2) belongs to the HK family, which is a group of serine proteases that includes PSA. HK2 shares 80% amino acid sequence identity with PSA. Both PSA and HK2 are predominantly expressed in the prostate and are regulated by both the action of androgens and a functional androgen receptor. Some studies have reported the overexpression of HK2 in prostate cancer tissue. HK2 has been studies in various combinations with free and total PSA to improve specificity and sensitivity for prostate cancer detection and prognosis, with mixed results (Reed, et al., 2010; Stephan, et al., 2010; Benchikh, et al., 2010). At this time, it is not available commercially and is not used in the clinical routine diagnosis of prostate cancer (Stephan, et al., 2010).

**Decipher™**

Decipher™ (GenomeDx Biosciences, San Diego, CA) that measures 22 genomic biomarkers associated with metastatic cancer to generate a result that indicates the likelihood of metastasis. The test proposes to classify an individual patient’s risk of clinical metastasis after radical prostatectomy. The test is available through ongoing clinical studies.

Badani et al. (2013) studied the influence on urologist treatment recommendations for 24 patients at risk of metastasis using a genomic-based prediction model (Decipher). A prospective, pre-post design was used to assess urologist treatment recommendations following radical prostatectomy (RP) in both the adjuvant (without any evidence of PSA rise) and salvage (biochemical recurrence [BCR]) settings. Urologists were presented de-identified pathology reports and genomic classifier (GC) test results for 24 patients from a previously conducted GC validation study in high-risk post-RP men. Treatment recommendations changed from pre-GC to post-GC in 43% of adjuvant, and in 53% of salvage setting case evaluations. In the adjuvant setting, urologists changed their treatment recommendations from treatment (i.e. radiation and/or hormones) to close observation post-GC in 27% of cases. For cases with low GC risk (<3% risk of metastasis), observation was recommended for 79% of the case evaluations post-GC. Consistent trends were observed in the salvage setting. Limitations of the study included the lack of randomization and the small number of patients.
There is insufficient evidence in the published peer-reviewed scientific literature to support the clinical utility of the Decipher test.

**Oncotype DX® Prostate Cancer ASSAY**

The Oncotype DX® Prostate Cancer ASSAY (Genomic Health, Redwood City, CA) is a multi-gene RT-PCR assay proposed to help determine the most appropriate treatment options. The most recent tissue sample (needle biopsy) is tested to algorithmically calculate the Genomic Prostate Score (GPS) to determine how likely the cancer is to be low risk or higher risk. The test measures the expression of 17 genes: FAM13C, KLK2, AZGP1, SRD5A2, BGN, COL1A1, SFRP4, ARF, ATP5E, CLTC, GPS1, PGK1, FLNC, GSN, TPM2, GSTM2, TPX2. Twelve genes are cancer related and five are reference genes. Oncotype DX is indicated for a man recently diagnosed with low- or intermediate-risk prostate cancer and has not started treatment. The results of the test are used in combination with the Gleason score and other clinical information (Genomic Health, 2013, Agency for Healthcare Research and Quality [AHRQ], 2013, Knezevic, et al, 2013). There is insufficient evidence to support the clinical utility of Oncotype DX for prostate cancer.

Oncotype DX was analytically and clinically validated in a study by Knezevic et al. (2013). Analytical accuracy was reported as “excellent” with average biases at qPCR inputs representative of patient samples < 9.7% across all assays. Amplification efficiencies were within ± 6% of the median. Ten prostate cancer RNA samples were tested for reproducibility and precision using multiple instruments, reagent lots, operators, days (precision), and RNA input levels (reproducibility) and appropriately parameterized linear mixed models.

The Blue Cross Blue Shield Technology Evaluation Center (TEC) published an assessment to examine the evidence available on two array-based gene expression analysis tests: Prolaris® (Myriad Genetics, Salt Lake City, UT) and Oncotype DX® Prostate (Genomic Health, Redwood City, CA) (TEC, 2013). The main purpose of the assessment is to address the incremental value of gene expression tests for discriminating men with aggressive and indolent disease to guide treatment decisions that improve net health outcomes. The evidence assessment addressed analytic validity, clinical validity, and clinical utility of each test. The primary study selection criterion was to include any peer-reviewed, full-length publication that reported evidence related to the analytic validity, clinical validity, or clinical utility of either test, using human prostate tumor specimens obtained by needle biopsy. The tests results from these two tests are intended to be used in combination with accepted clinical criteria (Gleason score, PSA, clinical stage) to stratify biopsy-diagnosed localized prostate cancer according to biological aggressiveness, and direct initial patient management. The authors found that direct evidence is insufficient to establish the analytic validity, clinical validity, or clinical utility of either test.

Based on the available evidence, the following judgments were made regarding whether array-based gene expression analysis meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to guide management of patients with newly diagnosed prostate cancer:

- The technology must have final approval from the appropriate governmental regulatory bodies: Neither Prolaris nor Oncotype Dx Prostate Cancer Assay is cleared for marketing by the U.S. Food and Drug Administration (FDA). Each is available under auspices of the Clinical Laboratory Improvement Act (CLIA).
- The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes:
  - The analytic validity has not been rigorously shown for either test under consideration here; it is indirectly suggested by results from the MicroArray Quality Control project, but remains to be specifically established.
  - Peer-reviewed evidence on the clinical validity of Prolaris comprises a retrospective cohort (n=349) culled from 6 cancer registries in Great Britain. No peer-reviewed, published evidence on the clinical validity of Oncotype Dx Prostate was identified. No evidence is available on the clinical utility of either test for any clinical endpoint.
- The technology must improve the net health outcome: Evidence is insufficient to determine whether Prolaris or Oncotype Dx Prostate testing affects the net health outcome.
- The technology must be as beneficial as any established alternatives: Evidence is insufficient to determine the incremental value of either Prolaris or Oncotype Dx Prostate gene expression test
compared with clinical criteria for discriminating men with aggressive and indolent disease to guide treatment decisions that improve the net health outcome.

- The improvement must be attainable outside the investigational settings: Evidence is insufficient to determine whether Prolaris or OncotypeDx Prostate testing improves health outcomes in the investigational setting.

Based on the above, the report determined that neither the Prolaris nor OncotypeDx Prostate array-based gene expression test meets the TEC criteria.

**Prolaris® (Myriad Genetics, Salt Lake City, UT)**

Prolaris is an array-based that is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a cell-cycle progression (CCP) score, or Prolaris score. It is proposed that this score can be used to estimate the risk of prostate cancer recurrence.

Please see above Blue Cross Blue Shield Technology Evaluation Center (TEC) report regarding a TEC assessment of the available evidence for Prolaris.

Cuzick et al. (2012) conducted a study to evaluate the prognostic value or a cell cycle progression signature for prostate cancer death. The study included a cohort of 349 men with clinically localized disease diagnosed by a needle biopsy and managed conservatively. A CCP score was calculated from expression levels of 31 genes. Clinical variables consisted of centrally re-reviewed Gleason score, baseline prostate-specific antigen level, age, clinical stage, and extent of disease. The primary endpoint was death from prostate cancer. In a univariate analysis, the hazard ratio (HR) for death from prostate cancer was 2.02 (95% CI [1.62, 2.53], P<10⁻⁵) for a one-unit increase in CCP score. The CCP score was only weakly correlated with standard prognostic factors and in a multivariate analysis, CCP score dominated (HR for one-unit increase=1.65, 95% CI (1.31, 2.09), P=3x10⁻⁵), with Gleason score (P=5x10⁻⁵) and prostate-specific antigen (PSA) (P=0.017) providing significant additional contributions. The authors concluded that for conservatively managed patients, the CCP score was a strong independent predictor of cancer death outcome. Limitations of the study included the lack of randomization, retrospective study, and needle biopsy provided a small portion of the tumor and limited amount of tissue from which to generate molecular data.

There is insufficient evidence in the published peer-reviewed scientific literature to support the clinical utility of the Prolaris test.

**Gene Hypermethylation/DNA methylation**

One of the epigenetic mechanisms that is considered to be involved in the development of prostate cancer is DNA methylation. Hypermethylation within the promoter region of tumor suppressor genes is an important mechanism of gene inactivation and has been described for many different tumor types. These type of alterations are also potentially reversible, unlike genetic alterations such as mutations, which may lead them being considered as possible targets for gene therapy (TEC, 2009). Currently, aberrant promoter hypermethylation has been investigated in specific genes from the following groups: tumor-suppressor genes, proto-oncogenes, genes involved in cell adhesion, and genes involved in cell-cycle regulation. Glutathione S-transferase P1 (GSTP1) has been shown to be a biomarker for prostate cancer. Other genes, e.g. CD44, PTGS2, E-cadherin, CDH13, and cyclin D2 have been found to be prognostic markers for prostate cancer (Phe, et al., 2010). The published studies are primarily small, retrospective pilot evaluations of hypermethylation status of various candidate genes for discriminating prostate cancer from benign conditions or for predicting disease recurrence and association with clinicopathologic predictors of aggressive disease (TEC, 2009).

**ConfirmMDx™**

ConfirmMDx (MDxHealth, Irvine, CA) is an epigenetic assay that is thought to detect an epigenetic field effect or “halo” associated with the cancerization process at the DNA level in cells adjacent to cancer foci. This epigenetic “halo” around a cancer lesion can be present despite having a normal appearance under the microscope. The assay investigates the methylation status of genes GSTP1, APC, and RASSF1 within residual prostate biopsy tissue for markers associated with malignancy. The test is purported to assist in distinguishing patients who have a true-negative biopsy from those who may have occult cancer. The test is performed on the prostate biopsy tissue.

Several retrospective studies have examined the use of gene methylation to detect prostate cancer (Van Neste, et al., 2012; Stewart, et al., 2013). These studies are preliminary and have not demonstrated the clinical utility of DNA methylation.
Single-nucleotide Polymorphisms (SNPs)

Single-nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. For a genetic variation to be considered a SNP, it must occur in at least 1% of the population. Many SNPs have no effect on cell function, but may help determine an individual’s risk of developing a particular disease, or influence response to a certain therapy. Potential candidate genes have been identified at three chromosomal loci (8q24, 17q12, and 17q24.3). Several large population studies have recognized SNPs that are highly significant predictors of prostate cancer risk, although the genes and biologic mechanisms behind these associations are as yet unidentified (Zheng, et al., 2008; Kote-Jarai, et al., 2008). Several SNPs combined appear to explain a considerable proportion of prostate cancer, but by no means all. A few different groups are commercializing specific SNP panels, combined in one case with family history, as risk assessment tools presumably to identify those men who should start disease surveillance early and be monitored frequently. At this time, these tests do not predict certainty of disease, nor do they clearly predict aggressive versus indolent disease. While the monitoring of high-risk men may improve outcomes, it is also possible that these could be offset by the harms of identifying and treating additional indolent disease (TEC, 2009).

The Agency for Healthcare Research and Quality (AHRQ) published a systematic review to address the evidence on the validity and utility of using SNP panels in the detection, diagnosis, and clinical management of prostate cancer (Little, et al., 2012). Fourteen articles were determined to be eligible. The eligibility criteria of the studies in the review included: English language studies; evaluating SNP analysis of human populations, or samples derived from human populations; the SNP analysis needed to be across more than one gene, be commercially available, and at least one of the gene variants included in the panel must have been validated in a genome-wide association (GWA) study. All but two evaluations were case-control studies, and were heterogeneous in terms of the composition of each SNP panel, the inclusion of other risk factor data, the populations in which they were evaluated, and the metrics used to judge the performance of the panel as a “test.” One evaluation was a cross-sectional study, and one was a cohort study of survival in men with prostate cancer. None of the studies were performed in routine clinical settings. Findings included:

- Regarding the analytic validity of currently available SNP-based panels designed for prostate cancer risk assessment:
  - The accuracy of assay results for individual SNPs in current panels: No direct assessment of the analytic validity of any SNP-based panels was identified in the literature search. From the articles that were identified as providing information relevant to the assessment of the clinical validity of SNP panels, no data on the analytic validity of individual SNPs that were components of the panels were presented.
  - The analytical validity of current panels whose purpose are, or includes, predicting the risk of prostate cancer: The reported accuracy rates ranged up to >99.9 percent. However, the methodologies described for determining analytical validity were not uniform across all analytes for some panels; in multiple cases, the SNP call rate of a given test panel was reported on the basis of data from two or more different chip platforms or analytical techniques. (For the purpose of the report—call rate defined as the proportion of samples for which genotypes are called for a converted marker).

- Regarding the clinical validity of currently available SNP-based panels designed for prostate cancer risk assessment:
  - The ability of available SNP-based genotyping panels to predict the risk of prostate cancer in terms of stratifying future risk and/or screening for current disease: the findings indicated that they were unlikely to be clinically useful.
  - The ability of available SNP-based genotyping panels to predict the risk of prostate cancer in terms of distinguishing between clinically important and latent/ asymptomatic prostate cancer; none of the evaluations suggested that that any of these panels performed well in distinguishing between more and less aggressive disease.
  - How well the available SNP-based genotyping panels predict prognosis in individuals with a clinical diagnosis of prostate cancer: There was no association between risk alleles and prostate cancer mortality for any of the panels and no increase of a model based on age, PSA, Gleason score, and tumor stage when SNPs panel data were added.
• Regarding the clinical utility of currently available SNP-based panels for prostate cancer risk assessment, in terms of the process of care, health outcomes, harms, and economic considerations: there were no eligible studies identified that addressed any component of clinical utility.

Although the studies indicate that there are genetic changes associated with prostate cancer, the studies published at this time are preliminary and do not provide evidence of the clinical utility of these tests or that they will affect clinical outcomes.

**Candidate Gene Panels for Prostate Cancer Diagnosis**
Since no single gene markers have been found that are both highly sensitive and highly specific for diagnosing prostate cancer, particularly in men that have an elevated PSA levels, some investigators are combining several promising markers into a single diagnostic panel. This may appear promising in concept, however, there is very limited evidence is available for these applications (TEC, 2009).

There is insufficient evidence found in the scientific literature regarding the use of candidate gene panels in prostate cancer diagnosis

**Professional Societies/Organizations**

**Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group:** The EGAPP Working Group published recommendations regarding prostate cancer antigen 3 (PCA3) testing for the diagnosis and management of prostate cancer and if the test improves patient health outcomes. The recommendation statement summarize the supporting scientific evidence from a complete evidence review performed by the Agency for Healthcare Research and Quality (AHRQ) which was used by the EGAPP Working Group to support recommendations regarding the use of PCA3 testing for diagnosis and management of prostate cancer (EGAPP, 2013; Bradley, et al., 2013).

The recommendations in the report included:

• Insufficient evidence found to recommend prostate cancer antigen 3 (PCA3) testing to inform decisions for when to rebiopsy previously biopsy-negative patients for prostate cancer or to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (e.g., previous elevated prostate-specific antigen test or suspicious digital rectal examination).

• Insufficient evidence to recommend PCA3 testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan.

• Based on the available evidence, the overall certainty of clinical validity to predict the diagnosis of prostate cancer using PCA3 is deemed “low.”

In the report, the EGAPP Working Group discourages clinical use for diagnosis unless further evidence supports improved clinical validity. Based on the available evidence, the overall certainty of net health benefit is deemed “low.” The EGAPP Working Group discourages clinical use unless further evidence supports improved clinical outcomes.

**National Comprehensive Cancer Network (NCCN):** The National Comprehensive Cancer Network Guidelines (NCCN Guidelines) published clinical practice guidelines for prostate cancer early detection (NCCN, 2012). They note that development of biomarkers, including PCA3, and kallikrein-related peptidase 2 (hK2) has been an ongoing interest. However, these tests have not been adequately evaluated as a primary screening test. The NCCN panelists do not recommend use of PCA3 as a genetic marker as negativity does not necessarily indicate negligible risk.

A NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology includes the following regarding PCA3, “Overall the inclusion of the PCA3 in multivariable models increased the predictive accuracy by up to 5.5%. These results, therefore, also indicate level IB* clinical validity, albeit with a modest improvement in diagnostic accuracy and insufficient evidence to determine the true clinical utility of this assay in routine clinical management.” (Febbo, et al., 2011)

*tumor marker utility grading system levels of evidence:
Level I: prospective, marker primary objective, well-powered or meta-analysis
Use Outside of the US

European Association of Urology (EAU): The EAU published updated guidelines on prostate cancer in 2012. The guidelines include the following regarding PCA3 testing (EAU, 2013):

- The PCA3 score increases with prostate cancer volume, but there is conflicting data about whether the PCA3 score independently predicts the Gleason score and its use as a monitoring tool in active surveillance has not been confirmed.
- The main current indication of the PCA3 urine test may be to determine whether a man needs a repeat biopsy after an initially negative biopsy outcome, but its cost-effectiveness remains to be shown.

The Canadian Urological Association (CUA): The CUA published guidelines for prostate cancer screening (Izawa, et al., 2011). Regarding PCA3, the guidelines note, “Biomarkers, such as PCA3, may play a more significant role in PCa screening, but the data supporting its use for routine screening is limited.”

Summary

Preliminary studies have shown PCA3 to be overexpressed in prostate tumors and that it may be quantified to distinguish between normal, benign hyperplastic and malignant conditions. The replicability and clinical utility of the PCA3 test have not been established at this time. Therefore, the role of gene-based (e.g., PCA3/DD3) testing for prostate cancer screening, detection and disease monitoring remains unknown at this time. Research is ongoing for several biomarkers that have been proposed for the screening, detection, and disease monitoring of prostate cancers. At this time, support from the professional societies and organizations is lacking, along with insufficient evidence in the published peer-reviewed scientific literature to support the use of gene-based testing for prostate cancer.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
   2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Experimental/Investigational/Unproven/Not Covered when used to report gene-based testing for prostate cancer screening, detection or disease monitoring:

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<td>S3721</td>
<td>Prostate cancer antigen 3 (PCA3) testing</td>
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References


70. Phé V, Cussennot O, Roupèrê M. Methylated genes as potential biomarkers in prostate cancer. BJU Int. 2010 May;105(10):1364-70.


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Coverage Policy Number: 0332


