



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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

Effective Date 4/15/2011
Next Review Date 4/15/2012
Coverage Policy Number 0332

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Hyperlink to Related Coverage Policies

- Circulating Tumor Cells Testing
- Prostate-Specific Antigen (PSA) Screening for Prostate Cancer
- Tumor Markers for Diagnosis and Management of Cancer

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Coverage Policy

CIGNA does not cover gene-based testing (e.g., PCA3\DD3) for prostate cancer for any indication including but not limited to screening, detection and/or disease monitoring because it is considered experimental, investigational or unproven.

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). 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.

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).

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

In September 2010, Gen-Probe Inc. (San Diego, CA) filed for Premarket Approval Application (PMA) to the US Food and Drug Administration (FDA) for the their test PROGENSA[®] PCA3 assay. The request is for use of the assay to test urine samples from men who previously have had a negative prostate biopsy. There are several laboratories in the U.S. are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing and offer PCA3 testing. The test is offered commercially based on reagents manufactured by Gen-Probe. Laboratories that offer PCA3 score testing include:

- AmeriPath Laboratories: offers PCA3 Profiler[®]
- Bostwick Laboratories: offers PCA3Plus[®]

Literature Review

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. Currently, PCA3 tests are undergoing validation (Parekh et al., 2007). 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).

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.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

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

CPT* Codes	Description
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83896	Molecular diagnostics; nucleic acid probe, each
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary

	procedure)
83902	Molecular diagnostics; reverse transcription
83912	Molecular diagnostics; interpretation and report
83913	Molecular diagnostics; RNA stabilization

ICD-9-CM Diagnosis Codes	Description
185	Malignant neoplasm of prostate
222.2	Benign neoplasm of prostate
233.4	Carcinoma in situ of prostate
236.5	Neoplasm of uncertain behavior of prostate
600.00 - 600.01	Hypertrophy (benign) of prostate
600.10 - 600.11	Nodular prostate
600.20 - 600.21	Benign localized hyperplasia of prostate
600.90 - 600.92	Hyperplasia of prostate, unspecified
602.3	Dysplasia of prostate
790.93	Elevated prostate specific antigen (PSA)
V10.46	Personal history of malignant neoplasm of prostate
V16.42	Family history of malignant neoplasm, prostate
V76.44	Special screening for malignant neoplasm of prostate
V84.03	Genetic susceptibility to malignant neoplasm of prostate
	All other codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	4/15/2008	0332	Gene-Based Testing for Prostate Cancer Screening, Detection and Disease Monitoring

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