Medical Policy

BlueCross BlueShield of Kansas
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Title: Gene-Based Tests for Screening, Detection, and/or Management of Prostate Cancer

Professional
Original Effective Date: February 11, 2011
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DESCRIPTION

There are a variety of gene-based biomarkers that have been associated with prostate cancer. These tests have the potential to improve the accuracy of risk prediction, diagnosis, staging, or prognosis of prostate cancer.

Background

Prostate cancer is a complex, heterogeneous disease. At the extremes of the spectrum, if left untreated, some prostate cancers behave aggressively, metastasize quickly, and cause mortality, while others are indolent and never progress to cause harm. Current challenges in prostate cancer care are risk assessment; early and accurate detection; monitoring low-risk patients undergoing surveillance only; prediction of recurrence after

initial treatment; detection of recurrence after treatment; and assessing efficacy of treatment for advanced disease.

In response to the need for better biomarkers for risk assessment, diagnosis, and prognosis, a variety of exploratory research is ongoing. Some products of this work have already been translated or are in the process of being translated into commercially available tests, including:

- single-nucleotide polymorphisms (SNPs) for risk assessment
- prostate cancer antigen 3 (PCA3) for disease diagnosis and prognosis
- transmembrane serine protease (TMPRSS) fusion genes for diagnosis and prognosis
- multiple gene tests (gene panels) for prostate cancer diagnosis
- gene hypermethylation for diagnosis and prognosis

While studies using these tests generate much information that may help elucidate the biologic mechanisms of prostate cancer and eventually help design treatments, the above-mentioned tests are in a developmental phase.

SNP testing as part of genome-scanning tests with risk assessments for prostate cancer are offered by a variety of laboratories including Navigenics, LabCorp (23andme), and ARUP (deCode) as laboratory-developed tests. The PCA3 test is offered in the U.S. by a number of reference laboratories including ARUP, Mayo Medical Laboratories, and LabCorp. The reagents used in testing are developed by Gen-Probe. The Prostate Gene Expression Profile was widely announced as available from Clarient, Inc. in January 2009; as of March 2011, the test no longer appears on the listing at the company website. A test for hypermethylation of GSTP1 is currently available from LabCorp ("Glutathione S-transferase Gene [GSTP1, pi-class] Methylation Assay"), and the required specimen is formalin-fixed, paraffin-embedded tissue. The test is stated to be an adjunct to histopathology. Epigenomics AG (Frankfurt, Germany) has entered licensing agreements with two U.S. laboratories (Quest and Predictive Biosciences) to establish and commercialize laboratory-developed tests for its proprietary methylation biomarker GSTP1. This test is not yet available, and it is unclear what matrices will be used.

Regulatory Status

Only PCA3 has been submitted to the U.S. Food and Drug Administration (FDA) for premarket approval. The Gen-Probe PROGENSA® PCA3 Assay was approved by the FDA on February 15, 2012 through the 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 PROGENSA PCA3 assay results."

The other tests mentioned in this policy, if available, are offered as laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories.

POLICY

Genetic tests for the screening, detection, and management of prostate cancer are considered **experimental / investigational**. This includes, but is not limited to the following:

1. single-nucleotide polymorphisms (SNPs) for risk assessment
2. PCA3 for disease diagnosis and prognosis
3. TMPRSS fusion genes for diagnosis and prognosis
4. multiple gene tests (gene panels) for prostate cancer diagnosis, or
5. gene hypermethylation for diagnosis and prognosis

RATIONALE

The most recent period of literature update covers the period of January 2012 through January 2013. This policy was primarily based on a 2008 TEC Special Report: "Recent Developments in Prostate Cancer Genetics and Genetic Testing." (1) The following text is based on the TEC Special Report and on relevant publications found subsequent to the TEC Special Report from MEDLINE literature searches.

In general, the evidence for genetic tests related to prostate cancer screening, detection, and management addresses either preliminary clinical associations between genetic tests and disease states. In some cases, the clinical validity of these tests, i.e., the association of the test result with outcomes of interest, is expressed in terms of sensitivity, specificity, predictive value, and/or comparisons to current standards using receiver-operating curve (ROC) analysis. There is no direct evidence of clinical utility, i.e., that using a test will change treatment decisions and improve subsequent outcomes that matter to the patient such as mortality, morbidity, or quality of life.

Single-nucleotide polymorphisms (SNPs) for risk assessment

Several large population studies have identified SNPs that are predictors of prostate cancer risk, although the genes and biologic mechanisms behind these associations are as yet unknown. In a review by Ioannidis et al., (2) 27 gene variants at a wide variety of chromosomal locations were identified that incurred additional risk for prostate cancer, although in all cases the incremental risk observed was modest (odds ratio [OR]: 1.36 or less). More recently Lindstrom et al., (3) in a study of 10,501 cases of prostate cancer and 10,831 controls, identified 36 SNPs showing association with prostate cancer risk including 2 (rs2735893 and rs266849) showing differential association with Gleason grade. Per allele odds ratios ranged from 1.07 to 1.44.

Because the SNPs individually provide relatively modest incremental information on both the occurrence of cancer and its behavior, investigators have begun to explore use of algorithms incorporating information from multiple SNPs to increase the clinical value of testing. Gudmundsson et al., (4) using 22 prostate cancer risk variants, estimated that carriers in the top 1.3% of the risk distribution have a 2.5 times increase in risk of developing disease compared to

the general population. Zheng et al. (5) identified 5 chromosomal regions in a Swedish population (2,893 patients with prostate cancer and 1,781 controls) and in conjunction with family history developed an algorithm which appeared to account for 46% of cases of prostate cancer. Salinas et al. (6) also evaluated use of 5 SNPs plus family history to predict risk of prostate cancer. While they identified a significant association in risk, they were unable to demonstrate improved models for assessing who is at risk of having or dying from prostate cancer, once known risk or prognostic factors are taken into account. Helfand et al. (7) developed an expanded algorithm using 9 genomic regions which identified patients with a 6-fold increase risk for prostate cancer. Two of the regions studied (2p15 and 11q13) were more likely to be associated with tumors with aggressive features.

Kader et al. evaluated a panel of 33 SNPs identified from GWAS associated with prostate cancer in 1,654 men. (8) Genetic score was a significant ($p<.001$) independent predictor of prostate cancer, with an odds ratio of 1.72 (95%confidence interval [CI]: 1.44-2.09) after adjustment for clinical variables and family history. Addition of genetic markers to the classification of prostate cancer risk resulted in 33% of men reclassified into a different risk quartile. Approximately half of these (n=267) were downgraded to a lower risk quartile, and the other half (n=265) were upgraded into a higher risk quartile. The net reclassification benefit was 10% ($p=0.002$). The authors concluded that with the additional information of genetic score, the same number of cancers could be detected by using 15% fewer biopsies.

Kim et al. published a meta-analysis evaluating 30 SNPs associated with prostate cancer in Caucasians (9). Odds ratios of between 1.12 and 1.8 were observed with 13 SNPs, which exhibited significant heterogeneity. The proportion of total genetic variance attributed by each SNP ranged between 0.2% and 0.9%, and the 30 SNPs in sum explained about 13.5% of the total genetic variance of the population at risk. Whether this level of performance has any impact on practice or outcomes remains an unanswered question.

Ishaak and Giri (10) performed a review of 11 replication studies involving 30 SNPs (19 in men of African descent and 10 in men with familial prostate cancer). Odds ratios were positively associated with prostate cancer, although the magnitude of association was generally small (ranging from 1.11 to 2.63).

To date, there has been no report of clinical validity for testing using standard terms for diagnostic use (e.g., sensitivity, specificity, positive or negative predictive values) and no evidence that testing has any impact on health outcomes.

New guidelines suggest that asymptomatic men with prostate specific antigen (PSA) results equal to or less than 3 ng/mL who will be regularly monitored by PSA testing should be given information on prostate cancer prevention with 5-alpha reductase inhibitors. (11) It is possible that future risk assessment assays with evidence supporting generalizability to a variety of populations will help identify those who would most benefit from preventive therapy.

Conclusions. There have been numerous studies demonstrating the association of many different SNPs with prostate cancer. These studies generally show a modest degree of association with future risk for prostate cancer. The clinical utility of these tests is uncertain, there is no evidence that the information obtained from SNP testing can be used to change management in ways that will improve outcomes.

PCA3 for prostate cancer diagnosis

PCA3 is overexpressed in prostate cancer and PCA3 mRNA can be detected in urine samples collected after prostate massage. When normalized using PSA to account for the amount of prostate cells released into the urine (PCA3 Score), the test has significantly improved specificity compared to PSA and may better discriminate patients with eventual benign findings on (first or second) biopsies from those with malignant biopsy results. In particular, the test may be especially helpful at identifying patients with elevated PSA levels but negative first biopsy results who need a follow-up biopsy. Based on several studies, (9, 12-16) average PCA3 Score sensitivity and specificity for a positive prostate biopsy result is about 61% and 74%, respectively.

Ankerst et al. (17) reported that incorporating the PCA3 Score into the Prostate Cancer Prevention Trial risk calculator improved the diagnostic accuracy of the calculator (from area under the curve [AUC]: 0.653 to AUC 0.696). Chun et al., (18) using a multivariate nomogram, demonstrated a 5% gain in predictive accuracy when PCA3 was incorporated with other predictive variables such as age, digital rectal examination (DRE) results, PSA levels, prostate volume, and past biopsy history. In a recent study of 218 patients with PSA values of 10 ng/mL or less, Perdona et al. (19) performed a head-to-head comparison of these two risk assessment tools and suggested both might be of value in clinical decision making.

Several studies have recently been focused on evaluating the PCA3 Score as a tool for distinguishing between patients with indolent cancers who may only need active surveillance and patients with aggressive cancers who warrant aggressive therapy. Haese et al., (15) Nakanishi et al., (20) and Whitman et al. (21) have all demonstrated an association between PCA3 Scores and evidence of tumor aggressiveness. However, Bostwick et al. (22) and vans Gils et al. (23) failed to confirm these findings. Auprich et al. (24) recently reported that PCA3 Scores appeared to enhance identification of indolent disease but not pathologically advanced or aggressive cancer.

A meta-analysis by Ruiz-Aragon and Marquez-Pelaez (25) reviewed 14 studies of PCA3 for use in predicting prostate biopsy results. Sensitivity of testing ranged from 46.9% to 82.3% and specificity from 56.3% to 89%. Global results provided a sensitivity of 85% (confidence interval [CI]: 84 to 87) and a specificity of 96% (CI: 96 to 97). No publications on how this information affected decision making or either short- of long-term outcomes has been published.

Tosoian et al. (26) reported on a short-term prospective cohort study evaluating PCA3 in relation to outcomes in an active surveillance program involving 294 subjects. PCA3 did not appear to distinguish patients with stable disease from those developing more aggressive features. Durand and colleagues found that PCA3 score offered some predictive prognostic accuracy in a cohort of 160 men. (27) PCA3 scores were significantly associated with increased tumor volume and positive surgical margins. However, in multivariate analysis, PCA3 score and Gleason score (>=7) did not emerge as independent predictors of pathologic stage.

Clinical utility studies using assay results for decision making for initial biopsy, repeat biopsy, or treatment have not been reported. A clinical trial (NCT01632930) aims to observe if the availability of the PCA3 test will reduce the number of unnecessary prostate biopsies in multiple French centers. The trial aims to enroll 650 participants with a completion date of June 2019.

Conclusions. Studies of PCA3 as a diagnostic test for prostate cancer report sensitivities and specificities in the moderate range. In general, these studies are preliminary and report on

clinical performance characteristics in different populations and at various assay cutoff values, reflecting the lack of standardization in performance and interpretation of PCA3 results. One study reports a modest incremental improvement in diagnostic accuracy when PCA3 was combined with PSA. The clinical utility of this test is uncertain, as there is no evidence that the use of PCA3 can be used to change management in ways that improves outcomes.

TMPRSS fusion genes for diagnosis and prognosis

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, ETV4, or ETV5), which modulates 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, suggesting a mechanism for neoplastic transformation. Fusion genes may be detected in tissue, serum, or urine,

TMPRSS2-ERG gene rearrangements have been reported in 50% or more of primary prostate cancer samples. (28)

While ERG appears to be the most common ETS family transcription factor involved in the development of fusion genes, not all are associated with TMPRSS2. About 6% of observed rearrangements are seen with SLC45A3, and about 5% appear to involve other types or rearrangement. (25)

TMPRSS2 fusion gene detection has been studied for prognostic value, e.g., to identify aggressive disease or to predict disease recurrence. There is conflicting evidence regarding the association of TMPRSS2 fusion gene detection and biochemical recurrence or survival outcomes of prostate cancer. (29-34) Subtypes of gene fusion may have more significant associations with biochemical recurrence. (32, 35, 36). TMPRSS2 fusion genes are strongly associated with higher disease stage, (22, 23, 30) but associations with Gleason scores (e.g., (30, 31, 33, 36, 37) are conflicting.

Most recently, increased attention has been directed at using post-DRE urine samples to look for fusion genes as a marker of prostate cancer. Laxman et al. (38) developed an assay to measure ERG and TMPRSS2: ERG transcripts in urine samples following prostatic massage from 19 patients with prostate cancer. They observed a strong concordance between the presence of these transcripts and prostate cancer. In a subsequent study of 234 patients presenting for biopsy or radical prostatectomy (138 with cancer; 86 with benign disease), these authors (39) confirmed the association between cancer and TMPRSS2: ERG but failed to demonstrate a significant association between cancer and ERG transcripts. An algorithm was created using 7 candidate biomarkers including SPINK1, PCA3, GOLPH2, and TMPRSS2: ERG. The AUC or this multiplex model was 0.785; sensitivity 66%, specificity 76%. Because the study was performed on a population enriched for cancer, external validation would be critical in properly defining and understanding test performance.

Rice et al. (26) developed an assay directed at evaluation of ERG RNA in urine normalized for PSA RNA. In a study of 237 men scheduled for prostate biopsy, this assay was found to identify cancer with an AUC of 0.592, a sensitivity of 31%, and specificity of 84%. Higher urine ERG values were associated significantly with a positive biopsy, although these did not correlate with

clinical stage or biopsy Gleason scores. Performance of the test was noted to be particularly good in Caucasian patients with a PSA value of 4 ng/mL or less. Adding ERG to results of PSA and other clinical parameters in a multivariate logistic regression model did not significantly improve performance in predicting biopsy. The authors conclude "further studies examining the long-term prognostic significance of these markers will show their full potential in augmenting the appropriate diagnosis and treatment of prostate cancer."

Tomlins et al. (40) have recently developed a transcription mediated amplification assay to measure TMPRSS2: EFG fusion transcript in parallel with PCA3. Combining results from these two tests and incorporating them into the multivariate Prostate Cancer Prevention Trial risk calculator appeared to improve identification of patients with clinically significant cancer by Epstein criteria and high-grade cancer on biopsy. While the study was large (1,312 men at multiple centers), it was confounded by the fact that the assay was modified during the course of the study and by the fact that some evaluations were performed using cross-validation rather than independent validation using independent training and testing sets. Further studies appear warranted.

Leyten et al. (41) investigated the predictive value of PCA3 and TMPRSS2 as individual biomarkers and as part of a panel in a prospective, multicenter study of 443 men. TMPRSS2 was found to be highly specific (93.2%) for predicting clinically significant prostate cancer on biopsy. Because of this high specificity, the authors suggest that rebiopsy or magnetic resonance imaging (MRI) be performed in EMPRSS2-ERG-positive patients who do not have prostate cancer detected on initial biopsy. The authors state that if these data pertaining to PCA3 and TMPRSS2 from the assay had been used to select men for prostate biopsy, 35% of biopsies could have been avoided.

Conclusions. Limited evidence reports that the measurement of TMPRSS:ERG may improve the ability to predict prostate cancer, and/or the ability to estimate prognosis. However, the results of available studies differ as to the accuracy of TMPRSS:ERG for this purpose. In addition, the clinical utility of this test is uncertain, i.e., there are no studies that report the test leads to changes in management that result in improved health outcomes.

Candidate gene panels for prostate cancer diagnosis

Because no single gene markers have been found that are both highly sensitive and highly specific for diagnosing prostate cancer, particularly in men already known to have elevated PSA levels, some investigators are combining several markers into a single diagnostic panel. While promising in concept, only single studies of various panels have been published, and none apparently is offered as a clinical service.

Clarient, Inc. launched a "patent protected combination of four genes that have been shown to accurately identify the presence of Grade 3 or higher" prostate cancer in prostate tissue in 2009. This test is reportedly based on a study that has been submitted for publication but has not yet been accepted for publication or available for evaluation. It appears that at this time Clarient, Inc. is not offering this assay.

Gene hypermethylation for diagnosis and prognosis

Epigenetic changes, chromatin protein modifications that do not involve changes to the underlying DNA sequence but which can result in changes in gene expression, have been identified in specific genes. There is an extensive literature reporting significant associations of

epigenetic DNA modifications with prostate cancer. Studies are primarily small, retrospective pilot evaluations of hypermethylation status of various candidate genes for discriminating prostate cancer from benign conditions (diagnosis) or for predicting disease recurrence and association with clinicopathologic predictors of aggressive disease (prognosis). A review of recently published studies (42) reveals an area of clinical research that has not yet identified the best markers for diagnosis and prognosis or the best way to measure them and in which sample type. No standardized assays and interpretation criteria have been agreed on yet to enable consistency and comparison of results across studies.

GSTP1 is the most widely studied methylation marker for prostate cancer, usually as a diagnostic application. Many studies have reported on the association of GSTP1 with prostate cancer. Two recent studies of GSTP1 hypermethylation using tissue samples reported significant results for identifying cancer with a sensitivity of 92%, a percent specificity of 85%, and an AUC of about 0.9. (43, 44) However, 2 other studies did not find significant associations with disease. (45, 46) In spite of these contradictory results, several investigators have evaluated detection of hypermethylation products in biological fluids for early detection of prostate cancer. Suh et al. (40) studied the ejaculates of patients with prostate cancer and observed methylated GSTP1 in 4 of 9 patients. Goessl et al. (47) confirmed the presence of the methylated biomarker in ejaculates (50%) and extended its evaluation to demonstrate an association with cancer in serum (82% of cancer patients), urine (36%), and urine following prostatic massage (73%).

Subsequently, Ellinger et al. (48) studied hypermethylation of GSTP1 with additional genes (T1G1, *Reprimo,* and PTGS2) in 226 patients (168 with prostate cancer) in an effort to provide a more consistent yield of positives. They observed that the detection of aberrant methylation in serum DNA has high specificity (92%) but variable and more modest sensitivity (42 to 47%) for cancer. Sunami et al. (49) assayed blood from 40 healthy individuals and 83 patients with prostate cancer using a 3-gene cohort (GSTP1, RASSF1, and RARβ2) and demonstrated a sensitivity of 28% for cancer patients.

In a recent meta-analysis of 30 peer reviewed studies evaluating hypermethylation of GSTP1 and other genes in prostate tissue, Van Neste et al. (50) suggest a valuable first step in diagnostic use might be to utilize testing for methylated genes in selecting patients undergoing a prostate biopsy who might not require a repeat biopsy.

Trock et al. (51) reported on a small (86 patient) diagnostic exploratory cohort study showing hypermethylation of adenomatous polyposis coli (APC) was associated with a high sensitivity and high specificity for cancer on repeat biopsy. There was no evidence suggesting how this test should be used to change management.

Stewart and colleagues investigated a quantitative methylation assay (including GSTP1, APC, and RASSF1) as a predictive test for occult prostate cancer. (52) The study retrospectively assayed 498 prostate biopsy tissue samples from patients who had negative histopathologic findings on first biopsy, but who received a follow-up biopsy within 30 months. The authors reported a sensitivity of 68% (95% CI: 57-77) and a specificity of 64% (95% CI: 59-69) for the assay score in predicting occult cancer. The negative predictive value of the test was 90% (95% CI: 87-93), which offered a significant improvement compared with histologic diagnosis alone (70% negative predictive value [NPV]). On multivariate analysis, the assay score was a significant predictor or prostate cancer on second biopsy, with an odds ratio of 3.17 (95% CI: 1.81–5.53, $p<0.0001$).

Conclusions. Studies reporting the diagnostic accuracy and predictive ability of gene hypermethylation report differing results regarding the accuracy of hypermethylation. These inconsistent results make it difficult to determine whether hypermethylation is a useful parameter for diagnosis and/or prognosis of prostate cancer. Further research is needed to elucidate the clinical validity of this test and to determine whether use of this test improves outcomes.

Summary
The evidence on the clinical validity of genetic tests related to prostate cancer screening, detection, and management is variable and incomplete, leaving considerable uncertainty regarding the clinical performance characteristics such as sensitivity, specificity, and predictive value. Some tests show evidence for predictive ability in the diagnosis or prognosis of prostate cancer; however, incremental accuracy in comparison to currently available tests has not been demonstrated. In addition, these data do not demonstrate clinical utility, i.e., that using a test will change treatment decisions and improve subsequent outcomes. Therefore, use of gene-based testing for risk assessment, diagnosis, prognosis, and management of prostate cancer is considered investigational.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

81479 Unlisted molecular pathology procedure
S3721 Prostate cancer antigen 3 (PCA3) testing.

- At this time, there are no specific CPT codes for this testing. The unlisted molecular pathology code 81479 would be used. Prior to 2013, a series of molecular diagnostic codes (83890-83912) would likely have been used.
- S3721 should be used for the Prostate cancer antigen 3 (PCA3) testing, effective 04-01-2012.

DIAGNOSES

Experimental / investigational for all diagnoses related to this policy.

REVISIONS

12-01-2011	Policy added to the bcbsks.com web site.
04-10-2012	In Coding section: Added HCPCS code: S3721 (effective 04-01-2012).
06-29-2012	Description section updated
	Rationale section updated
	References updated

01-01-2013	In Coding section: ▪ Added CPT code: 81479 (effective 01-01-2013) ▪ Removed CPT codes: 83890, 83891, 83892, 83893, 83894, 83896, 83897, 83898, 83900, 83901, 83902, 83903, 83904, 83905, 83906, 83907, 83908, 83909, 83912 (effective 12-31-2012)
08-20-2013	Description section reviewed with no changes made.
	Rationale section updated
	In Coding section: ▪ Coding instructions added.
	References updated

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