

Medical Policy Manual

Topic: Gene-Based Tests for Screening, Detection, and/or Management of Prostate Cancer

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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.

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
- The Gen-Probe PROGNSA® PCA3 Assay (PCA3) for disease diagnosis
- TMRSS 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 currently in a developmental phase, without evidence of clinical utility for diagnosis, prognosis, or risk assessment. The majority of tests listed above have not been submitted to the U.S. Food and Drug Administration (FDA) for marketing clearance but, if available, are offered as laboratory-developed tests by Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories.

SNP testing as part of genome-scanning tests with risk assessment 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 Clariant, 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 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 the PCA3 has been submitted to the U.S. Food and Drug Administration (FDA) for premarket approval. The PCA3 Assay was approved by the FDA on February 15, 2012 through the premarket approval process. According to the approval granted by the FDA:^[1]

“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.”

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

MEDICAL POLICY CRITERIA

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

- A. Single-nucleotide polymorphisms (SNPs) for risk assessment;
- B. PCA3 for disease diagnosis;
- C. TMPRSS fusion genes for diagnosis and prognosis;

- D. Multiple gene tests (gene panels) for prostate cancer diagnosis; or
- E. Gene hypermethylation for diagnosis and prognosis.

SCIENTIFIC EVIDENCE

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 or, in some cases, the clinical validity of these tests, i.e., the association of the test result with outcomes of interest, expressed in terms of clinical performance characteristics such as sensitivity, specificity, predictive value, and comparisons to current standards using receiver-operating curve (ROC) analysis and/or logistic regression. There is no 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.

Gene-Based Tests in General

A 2009 BlueCross BlueShield Association (BCBSA) TEC Special report of recently published studies on gene-based tests (SNPs, PCA3, TMPRSS, gene panels, and gene hypermethylation) for prostate cancer risk assessment and diagnosis concluded that, in general, research on these tests is still in a “developmental phase, currently without evidence of clinical utility.”^[2]

Single-Nucleotide Polymorphisms (SNPs)

There have been numerous large observational correlational studies focusing on the association of many different SNPs with prostate cancer, an example of which includes the study by Lindstrom and colleagues of 10,501 cases of prostate cancer and 10,831 controls, which identified 36 SNPs showing association with prostate cancer risk including two (rs2735893 and rs266849) showing differential association with Gleason grade. Per allele odds ratios ranged from 1.07 to 1.44.^[3]

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. Several such recent studies focused on the development of testing algorithms incorporating SNPs.^[4-7] A systematic review of population-derived correlations (not addressing clinical utility) has also been published.^[8] In a recent study, Kader et al. evaluated a panel of 33 SNPs identified from GWAS associated with prostate cancer in 1,654 men.^[9] Genetic score was a significant ($p < .001$) independent predictor of prostate cancer, with an odds ratio of 1.72 (95% 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. However, this study includes a limited sample size and there is no clear indication of how clinical management changed when patients were reclassified into lower risk groups.

Conclusion

As in the Kader study, available evidence generally reports a modest association with future risk for prostate cancer, such associations have not been studied in a clinical setting. 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 value).

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

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 been proposed for use in discriminating between 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.

Systematic Review/Meta-analysis

- In a recent systematic review, authors discuss the potential use of genetic markers to better define groups of men at high risk of developing prostate cancer, to improve screening techniques, discriminate indolent versus aggressive disease, and improve therapeutic strategies in patients with advanced disease.^[10] Genetic tests for PCA3 and TMPRSS2-ERG genes were included. Authors concluded that most markers have not been prospectively validated for providing useful prognostic or predictive information or improvement upon clinicopathologic parameters already in use.
- A meta-analysis by Ruiz-Aragon and Marquez-Pelaez reviewed 14 studies of PCA3 for use in predicting prostate biopsy results.^[11] Sensitivity of testing ranged from 47% to 82% and specificity from 56% 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- or long-term outcomes has been published.

Non-randomized Trials

Results from several studies have indicated the potential for improved diagnostic accuracy of standard risk assessment tools with addition of the PCA3 test.^[12-14]

However, among studies 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, results are divergent. Several studies have found evidence for an association between PCA3 Scores and tumor aggressiveness,^[15-18] while others either failed to find any association,^[19-21] or reported that PCA3 Scores appeared to enhance identification of indolent disease but not pathologically advanced or aggressive cancer.^[22,23]

In general, these studies are preliminary and reported 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. At present, 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 improve outcomes.

Conclusion

There is a lack of standardization in performance and interpretation of PCA3 results. The PCA3 studies are preliminary and report on clinical performance characteristics in different populations and at various assay cutoff values. 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

TMPRSS2 fusion gene detection has been studied for prognostic value, e.g., to identify aggressive disease or to predict disease recurrence. 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 (TMPRSS2-ERG).

No studies of clinical utility have been published to date; the evidence consists of correlational studies (association between a fusion gene and prostate cancer).^[21,24-26] However, the results of available studies differ as to the accuracy of TMPRSS-ERG in improving the ability to predict prostate cancer, and/or the ability to estimate prognosis for this purpose. In a recent study by Leyten et al., the predictive value of PCA3 and TMPRSS2 as individual biomarkers and as part of a panel in a prospective, multicenter study of 443 men was investigated.^[27] TMPRSS2 was found to be highly specific (93.2%) for predicting clinically significant prostate cancer on biopsy. The authors state that if this data pertaining to PCA3 and TMPRSS2 from the assay had been used to select men for prostate biopsy 35% of biopsies could be avoided. However, the clinical utility of this test is uncertain, as there are no studies that report the test leads to changes in management that result in improved health outcomes.

Conclusion

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

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, diagnostic panels have not been sufficiently studied and are not currently offered as a standard clinical service.

A comparative effectiveness report funded by the Agency for Healthcare Research and Quality (AHRQ) assessed the use of SNP-based panels for prostate cancer risk assessment.^[28] Following an extensive literature search, the report concluded that low estimates of diagnostic accuracy indicate that current panels “have poor discriminative ability.” As analytical validity is a prerequisite for clinical utility, the review concluded there is currently no evidence to support the clinical utility of these panels.

Gene Hypermethylation

Epigenetic changes, chromatin protein modifications that do not involve changes to the underlying DNA sequence but which can result in changes in gene expression (particularly expression of genes associated with prostate cancer), have been identified in specific genes. Studies are primarily small, retrospective pilot evaluations of hypermethylation status of various candidate genes (GSTP1, TIG1, Reprimo, PTGS2, RASSF1, and RAR β 2, among others) for discriminating prostate cancer from benign conditions (diagnosis), several of which have found significant associations^[26,29-36] and several of which have not found evidence of an association.^[37,38] Nevertheless, no standardized assays and interpretation criteria have been agreed on yet to enable consistency and comparison of results across studies.

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.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines on the early detection of prostate cancer state, “the development of biomarkers has been an ongoing interest.^[39] Examples are urinary prostate cancer antigen 3 (PCA3) and kallikrein-related peptidase 2 (hK2). However, these have not been adequately evaluated as a primary screening test. Panelists do not recommend use of PCA3 as a genetic marker as negativity does not necessarily indicate negligible risk.” Further NCCN guidelines on prostate cancer do not address gene-based tests for screening, detection, and/or management of prostate cancer.^[40]

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.

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CROSS REFERENCES

[Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20

[Microarray-based Gene Expression Analysis for Prostate Cancer](#), Genetic Testing, Policy No. 71

CODES	NUMBER	DESCRIPTION
CPT	None	
HCPCS	S3721	Prostate cancer antigen 3 (PCA3) testing