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Medical Policy Manual

Topic: Microarray-based Gene Expression Analysis for Prostate Cancer

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Section: Genetic Testing

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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

Gene expression profile analysis has been proposed as a means to risk-stratify patients with low-risk prostate cancer, diagnosed by needle biopsy, to guide treatment decisions.

Background

Localized prostate cancers may appear very similar clinically at diagnosis.[1] However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (e.g., D'Amico criteria) or prognostic tools that are based on clinical findings including PSA titers, Gleason grade, or tumor stage.[2-6] In studies of conservative management, the risk of localized disease progression based on prostate cancer-specific survival rates at 10 years may range from 15% [7,8]to 20%[9] to perhaps 27% at 20-year follow-up.[10] Among elderly men (aged 70 years or more) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men die with prostate cancer present, rather than from the cancer. Other very similar-appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

The divergent behavior of localized prostate cancers creates uncertainty about whether or not to treat immediately.[11,12] A patient may choose definitive treatment upfront, such as surgery (radical prostatectomy), external-beam radiation therapy (EBRT), brachytherapy, high-intensity-focused

ultrasound, systemic chemotherapy, hormonal therapy, cryosurgery, or combinations are used to treat patients with prostate cancer.[12-14] Complications associated with those treatments most commonly reported (radical prostatectomy, EBRT) and with the greatest variability were incontinence (0-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically 5% or less); gastrointestinal and bowel toxicity including nausea and loose stools (25-50%); proctopathy, including rectal pain and bleeding (10-39%); and erectile dysfunction including impotence (50-90%).[14]

In addition, the American Urological Association (AUA) guidelines for the management of clinically localized prostate cancer suggest that patients with low- and intermediate-risk disease have the option of "active surveillance", taking into account patient age, patient preferences, and health conditions related to urinary, sexual, and bowel function.[14] With this approach the patient forgoes immediate therapy and continues regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.[15,16]

Given the unpredictable behavior of early prostate cancer, additional prognostic methods to biologically stratify this disease are under investigation. These include microarray-based gene expression profiling, which refers to analysis of mRNA expression levels of many genes simultaneously in a tumor specimen.[17-22] Two microarray-based gene expression profiling tests to biologically stratify prostate cancers are currently available, Prolaris® (Myriad Genetics) and Oncotype DX® Prostate Cancer Assay (Genomic Health). Both use archived tumor specimens as the mRNA source, reverse transcriptase polymerase chain reaction amplification, and the TaqMan low-density array platform (Applied Biosystems). Prolaris® is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score. Oncotype DX® Prostate is used to quantify expression levels of 12 cancer-related and 5 reference genes to generate a Genomic Prostate Score (GPS). In the final analysis, the CCP score or GPS are combined in proprietary algorithms with clinical risk criteria (PSA, Gleason grade, tumor stage) to generate new risk categories (i.e., reclassification) intended to reflect biological indolence or aggressiveness of individual lesions, and thus inform management decisions.

Regulatory Status

Neither Prolaris® or Oncotype DX® Prostate Cancer Assay are cleared for marketing by the U.S. Food and Drug Administration (FDA). Each is available under the auspices of the Clinical Laboratory Improvement Act (CLIA). Clinical laboratories may develop and validate tests in-house (laboratory-developed tests [LDTs]) and market them as a laboratory service; LDTs must meet the general regulatory standards of the CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

Gene expression analysis to guide management of prostate cancer is considered **investigational** in all situations, including but not limited to the following tests:

1. Oncotype DX® Prostate Cancer Assay
2. Prolaris®

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on 3 main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

This policy is based on a 2013 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment with a literature review through June 2013.[23] Full-length publications were sought that described the analytic validity, clinical validity, and clinical utility of either Prolaris® or Oncotype DX® Prostate gene expression profiling. Evidence was reviewed on the use of either test to predict the aggressiveness or indolence of newly biopsy-diagnosed localized prostate cancer.

Analytic Validity

The analytic validity is the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent.

No published data on the analytic validity of Prolaris® were identified. In the only study of validity for the Oncotype DX® Prostate test, authors from Genomic Health, Inc., the developer of the test, reported analytical accuracy and reproducibility.[24] These outcomes will require validation in additional studies, preferably from independent investigators. Information was available on the performance of the TaqMan array platform (Applied Biosystems) used in Prolaris® and Oncotype DX® Prostate from the MicroArray Quality Control (MAQC) project.[25] In the MAQC project, initiated and led by FDA scientists, expression data on 4 titration pools from 2 distinct reference RNA samples were generated at multiple test sites on 7 microarray-based and 3 alternative technology platforms including TaqMan. According to the investigators, the results provided a framework to assess the potential of array technologies as a tool to provide reliable gene expression data for clinical and regulatory purposes. The results showed very similar performance across platforms, with a median coefficient of variation of 5% to 15% for the quantitative signal and 80% to 95% concordance for the qualitative detection call between sample replicates.

Clinical Validity

The clinical validity of a test is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease.

Polaris

One full-length, peer-reviewed article reported a validation study of Prolaris to determine its prognostic value for prostate cancer death in a conservatively managed needle biopsy cohort.[26] Cuzick et al. reported the results of a validation study of Prolaris® to determine its prognostic value for prostate cancer death in a conservatively managed needle biopsy cohort. The authors did not state whether this study adhered to the PRoBE (prospective-specimen-collection, retrospective-blinded evaluation) criteria suggested by Pepe and colleagues for an adequate biomarker validation study.[27] They noted that the cell cycle expression data were read blind to all other data, which conformed to the criteria; however, patients were identified retrospectively from tumor registries and there were no case-control subjects, which does not conform to the criteria.

Patients with clinically localized prostate cancer diagnosed by needle biopsy between 1990 through 1996 were identified in 6 registries. Additional inclusion criteria included age younger than 76 years at diagnosis, available baseline prostate-specific antigen (PSA) measurement, and conservative management.[28] Exclusion criteria included radical prostatectomy, death, evidence of metastatic disease within 6 months of diagnosis, or hormone therapy prior to diagnostic biopsy. A cell cycle progression (CCP) score consisting of expression levels of 31 predefined cell cycle progression genes and 15 housekeeper genes was generated using TaqMan low-density arrays. The values of each of the 31 CCP genes were normalized by subtraction of the average of up to 15 nonfailed housekeeper genes for that replicate.

Of 776 patients diagnosed by needle biopsy, 349 (79%) produced a CCP score and had complete baseline and follow-up information. The median potential follow-up time was 11.8 years during which a total of 90 deaths from prostate cancer occurred within 2799 person-years of actual follow-up. The main assessment of the study was a univariate analysis of the association between death from prostate cancer and the CCP score. A further predefined assessment of the added prognostic information after adjustment for the baseline variables was also undertaken. The primary end point was time to death from prostate cancer. A number of covariates were evaluated: centrally reviewed Gleason primary grade and score; baseline PSA value; clinical stage; extent of disease (percent of positive cores); age at diagnosis; Ki-67 immunohistochemistry; and initial treatment. The results are shown in Table 1.

Table 1. Univariate and Multivariate Analysis for Death From Prostate Cancer in the Cuzick 2012 Validation Study

Variable	N	Univariate	Multivariate
		Hazard Ratio (95% CI)	**Hazard Ratio (95% CI)**
1-unit increase in CCP score	349	2.02 (1.62 to 2.53)	1.65 (1.31 to 2.09)
Gleason score			
<7	106	0.46 (0.25 to 0.86)	0.61 (0.32 to 1.16)
7	152	Referent	Referent
>7	91	2.70 (1.72 to 4.23)	1.90 (1.18 to 3.07)
log (1+PSA)/(ng/mL)	349	1.70 (1.31 to 2.20)	1.37 (1.05 to 1.79)
Proportion of positive cores			
<50%	69	0.50 (0.22 to 1.12)	
50 to <100%	106	Referent	
100%	160	1.66 (1.01 to 2.73)	
Age at diagnosis (y)	349	1.00 (0.96 to 1.04)	
Clinical stage			
T1	38	0.75 (0.32 to 1.75)	
T2	106	Referent	
T3	43	1.74 (0.90 to 3.38)	
Hormone use			
No	200	Referent	

Yes	149	1.97 (1.30 to 2.98)	

CI: confidence interval

The median CCP score was 1.03 (IQ range, 0.41-1.74). The primary univariate analysis suggested that a 1-unit increase in CCP score was associated with a 2-fold increase in the risk of dying from prostate cancer. In preplanned multivariate analyses, extent of disease, age, clinical stage, and use of hormones had no statistically significant effect on risk; only the Gleason score and PSA remained in the final model. Further exploratory multivariate modeling to produce a combined score, including CCP, Gleason score, and PSA level, suggested a strong, predominant nonlinear influence of the CCP score in predicting the risk of death from prostate cancer (p=0.008).

Cuzick and colleagues suggested this combined score provided additional discriminatory information to help identify low-risk patients who could be safely managed by active surveillance. For example, among patients with a Gleason score of 6, for whom uncertainty existed as to the appropriate management approach, the predicted 10-year prostate cancer death rate ranged from 5.1% to 20.9% based on Gleason score and PSA; the range when assessed against the combined CCP, Gleason, and PSA score was 3.5% to 41%. However, the authors cautioned that because death rates were rare in this group, larger cohorts would be required to fully assess the value of the CCP combined score.

Table 2 shows Kaplan-Meier analyses of 10-year risk of prostate cancer death stratified by CCP score groupings. Cuzick et al. reported no significance tests for the estimates. Nor did they explain the apparent substantial difference in mortality rates among patients in the $0 \leq CCP \leq 2$ grouping (range, 19.3-21.1%) and those in the $2 < CCP \leq 3$ and > 3 groupings (range, 48.2-74.9%). The difference may simply reflect clinical criteria, for example, proportions of lower compared with higher Gleason grade cancers, respectively.

Table 2. Kaplan-Meier Estimates of Prostate Cancer Death at 10 Years According to CCP Score Groupings in the Cuzick 2012 Validation Study

CCP Score Group	N	10-Year Death Rate (%)
$CCP \leq 0$	36	19.3
$0 < CCP \leq 1$	133	19.8
$1 < CCP \leq 2$	114	21.1
$2 < CCP \leq 3$	50	48.2
> 3	16	74.9

Oncotype DX® Prostate

No published data on the clinical validity of Oncotype DX Prostate were identified. An abstract of a clinical validation study was presented at the 2013 annual meeting of the American Urological Association, but slides are not available. According to the Genomic Health website, in collaboration with the University of California San Francisco (UCSF), evaluation was done for the Oncotype DX Prostate test on needle biopsy tissue from patients who could have been candidates for active surveillance but underwent radical prostatectomy. These results were then correlated to their radical prostatectomy specimens. This information is insufficient to assess the clinical validity of this test.

Clinical Utility

The clinical utility describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

No published data on the clinical utility of Prolaris® or Oncotype DX® Prostate were identified. At present, no conclusions can be reached on this topic.

Clinical Practice Guidelines

No clinical practice guidelines or position statements from U.S. professional societies were found that address this testing.

Summary

There is currently no published evidence on how microarray-based gene expression testing alters clinical practice and clinical health outcomes (clinical utility) in patients with prostate cancer. Additionally, there are no evidence-based clinical practice guidelines which recommend the use of these tests for the management of prostate cancer. Therefore, gene expression analysis for prostate cancer management is considered investigational.

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CROSS REFERENCES

Gene-Based Tests for Screening, Detection and/or Management of Prostate Cancer, Genetic Testing, Policy No. 17

CODES	NUMBER	DESCRIPTION
CPT	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	