



Kansas City

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## Gene Expression Profile Analysis for Prostate Cancer Management

**Policy Number:** 2.04.111

**Origination:** 04/2014

**Last Review:** 04/2014

**Next Review:** 04/2015

### **Policy**

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Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Gene Expression Profile Analysis for Prostate Cancer Management. This is considered investigational.

### **When Policy Topic is covered**

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Not Applicable

### **When Policy Topic is not covered**

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Gene expression analysis to guide management of prostate cancer is considered **investigational** in all situations.

### **Considerations**

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There is no specific CPT code for this testing. Both of the currently available tests utilize analysis of the results of testing for multiple genes with an algorithm and with the results reported as a type of score. Therefore, the unlisted multianalyte assay with algorithmic analysis (MAAA) unlisted code 81599 should be reported.

### **Description of Procedure or Service**

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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**

Prostate cancer is the second most common cancer diagnosed among men in the U.S. According to the National Cancer Institute (NCI), nearly 240,000 new cases are expected to be diagnosed in the U.S. in 2013, and associated with around 30,000 deaths. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years.(1) However, NCI Surveillance Epidemiology and End Results data show age-adjusted cancer-specific mortality rates for men with prostate cancer have declined from 40 per 100,000 in 1992 to 22 per 100,000 in 2010. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Localized prostate cancers may appear very similar clinically at diagnosis.(2) However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (eg, D'Amico criteria) or prognostic tools that are based on clinical findings, including PSA titers, Gleason grade, or tumor stage.(3-7) 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%(8,9) to 20%(10) to perhaps 27% at 20-year follow-up.(11) Among elderly men (70 years or more) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will 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 whether or not to treat immediately.(12,13) A patient may choose definitive treatment upfront.(14) 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.(13,15) 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%).(15)

American Urological Association (AUA) Guidelines suggest 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.(15) With this approach the patient will forgo immediate therapy and continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.(16,17)

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.(18-23) Two microarray-based gene expression profiling tests are now offered, intended to biologically stratify prostate cancers: Prolaris® (Myriad Genetics, Salt Lake City, UT) and Oncotype Dx® Prostate Cancer Assay (Genomic Health, Redwood City, CA). Both use archived tumor specimens as the mRNA source, reverse transcriptase polymerase chain reaction amplification, and the TaqMan low-density array platform (Applied Biosystems, Foster City, CA). 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 (ie, reclassification) intended to reflect biological indolence or aggressiveness of individual lesions, and thus inform management decisions.

### **Regulatory Status**

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 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.

### **Rationale**

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This policy is based on a 2013 TEC Assessment with a literature review through June 2013.(24) 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. We reviewed evidence on the use of either test to predict the aggressiveness (or indolence) of newly diagnosed (by needle biopsy), localized prostate cancer.

**Analytic Validity** (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

Published data on the analytic validity of Prolaris® or OncotypeDx® Prostate was not identified. Information is available on the performance of the TaqMan array platform (Applied Biosystems, Foster City, CA) used in Prolaris® and Oncotype Dx® Prostate through 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 provide 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 diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

Prolaris®

One full-length, peer-reviewed article reports results of 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. did not state whether this study adheres to the PROBE (prospective-specimen-collection, retrospective-blinded evaluation) criteria suggested by Pepe et al for an adequate biomarker validation study.(27) They note that the cell cycle expression data were read blind to all other data, which conforms to the criteria; however, patients were identified retrospectively from tumor registries, and there were no case-control subjects, which does not conform.

Patients were identified from 6 cancer registries in Great Britain and were included if they had clinically localized prostate cancer that was diagnosed by needle biopsy between 1990 through 1996; were younger than 76 years at diagnosis; had a baseline prostate-specific antigen (PSA) measurement; and were conservatively managed. Potentially eligible patients who underwent radical prostatectomy, died, or showed evidence of metastatic disease within 6 months of diagnosis were excluded. Those who received hormone therapy prior to diagnostic biopsy also were excluded. The original biopsy specimens were retrieved and centrally reviewed by a panel of expert urological pathologists to confirm the diagnosis and, where necessary, to reassign Gleason scores by use of a contemporary and consistent interpretation of the Gleason scoring system.(28)

Tumor cells were microdissected from needle biopsy blocks, the amount determined by the length of the cancer available in the core and to enable preservation of any remaining cancer tissue for tissue microarray studies. 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 and for which a section was available to review histology, needle biopsies were retrieved for 527 (68%), 442 (84%) of which had adequate material to assay. Among the 442, a proportion, 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 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. (26) 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
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		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
<b>1-unit increase in CCP score</b>	349	2.02 (1.62 to 2.53)	1.65 (1.31 to 2.09)
<b>Gleason score</b>			
<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)
<b>log (1+PSA)/(ng/mL)</b>	349	1.70 (1.31 to 2.20)	1.37 (1.05 to 1.79)
<b>Proportion of positive cores</b>			
<50%	69	0.50 (0.22 to 1.12)	
50 to <100%	106	Referent	
100%	160	1.66 (1.01 to 2.73)	
<b>Age at diagnosis (y)</b>	349	1.00 (0.96 to 1.04)	
<b>Clinical stage</b>			
T1	38	0.75 (0.32 to 1.75)	
T2	106	Referent	
T3	43	1.74 (0.90 to 3.38)	
<b>Hormone use</b>			
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 suggests 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 suggest this combined score provides 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 exists 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%. They caution, however, that because death rates were rare in this group, larger cohorts are required to fully assess the value of the CCP combined score.

Kaplan-Meier analyses of 10-year risk of prostate cancer death stratified by CCP score groupings are shown in Table 2. 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  $0 \leq \text{CCP} \leq 2$  grouping (range, 19.3-21.1%) and those in the  $2 < \text{CCP} \leq 3$  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
$0 < \text{CCP} \leq 1$	133	19.8
$1 < \text{CCP} \leq 2$	114	21.1
$2 < \text{CCP} \leq 3$	50	48.2
$> 3$	16	74.9

### Oncotype Dx® Prostate

No full-length publications on the clinical validity of Oncotype Dx® Prostate were identified. The Genomic Health website presents information on gene panel development studies and a clinical validation study that was performed to evaluate this test in specimens obtained by needle biopsy in a cohort of men in the U.S. The latter study was presented at the 2013 annual meeting of the American Urological Association, but slides are not available (abstract 2131 at [http://www.aa2013.org/abstracts/archive/abstracts\\_POD35.cfm](http://www.aa2013.org/abstracts/archive/abstracts_POD35.cfm)). According to the website, the developer of the test and their collaborators from the University of California San Francisco (UCSF) evaluated the Oncotype Dx® prostate test on needle biopsy tissue from patients who could have been candidates for active surveillance but underwent radical prostatectomy, then correlated the biopsy results to their radical prostatectomy specimens. This information is insufficient to assess the clinical validity of this test.

**Clinical Utility** (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.

### **Section Summary**

The analytic validity of gene expression analysis for prostate cancer management 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. In the primary univariate analysis, a 1-unit increase in CCP score was associated with a 2.02-fold (95% confidence interval [CI], 1.62 to 2.53,  $p=8.6 \times 10^{-10}$ ) increase in the hazard of death from prostate cancer at 10-year follow-up. Multivariate analyses showed only the CCP score (hazard ratio [HR] for a 1-unit increase in CCP score = 1.65; 95% CI, 1.31 to 2.09;  $p=2.6 \times 10^{-5}$ ), Gleason score  $<7$  (HR=0.61; 95% CI, 0.32 to 1.16;  $p=5.0 \times 10^{-4}$ ) and prostate-specific antigen (PSA) titer (HR=1.37; 95% CI, 1.05 to 1.79;  $p=0.017$ ) were statistically associated with prostate cancer-specific mortality at 10 years. The investigators assert the CCP score alone was more prognostic than either PSA titer or Gleason score for tumor-specific mortality at 10-year follow-up. Although the patients may be similar to those of a modern U.S. cohort, comparability is unclear from the

single publication that is available. Furthermore, the study is limited by the use of archived biopsy specimens, with attendant issues of reproducibility and test reliability.

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 end point.

### **Ongoing Clinical Trials**

No active clinical trials were identified in a search of the [Clinicatrials.gov](http://www.clinicaltrials.gov) website as of October 14, 2013.

### **Summary**

Two gene expression analysis tests—Prolaris® and Oncotype Dx® Prostate—are commercially available. The test results are intended to be used in combination with accepted clinical criteria (Gleason score, prostate-specific antigen [PSA], clinical stage) to stratify biopsy-diagnosed localized prostate cancer according to biological aggressiveness, and direct initial patient management. Direct evidence is insufficient to establish the analytic validity, clinical validity, or clinical utility of either test. Therefore, gene expression analysis for prostate cancer management is considered investigational.

### **Practice Guidelines and Position Statements**

None identified.

### **Medicare National Coverage**

The Prolaris test will be denied as not reasonable and necessary regardless of the diagnosis billed ([http://www.findacode.com/medicare/policies-guidelines/display-medicare-info.php?type=ARTICLE&type\\_id=52156](http://www.findacode.com/medicare/policies-guidelines/display-medicare-info.php?type=ARTICLE&type_id=52156))

No national coverage determination for the Oncotype Dx® Prostate test was identified.

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### **Billing Coding/Physician Documentation Information**

**81599** Unlisted multianalyte assay with algorithmic analysis

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### **Additional Policy Key Words**

N/A

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### **Policy Implementation/Update Information**

4/1/14 New policy; considered investigational

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State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.