Systems Pathology in Prostate Cancer

Policy # 00286
Original Effective Date: 02/16/2011
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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of tests utilizing systems pathology that include cellular and biologic features of a tumor, including use in predicting risk of recurrence in patients with prostate cancer to be **investigational.***

Background/Overview

Predicting risk of recurrence in patients undergoing treatment for prostate cancer is difficult, as it is for most malignancies. Over time, risk models for patients with prostate cancer have evolved from early efforts that relied on grade, stage, and prostate-specific antigen (PSA) levels to complex multivariate models. A publication in 2008 indicates that there are more than 65 published, externally validated prostate cancer nomograms and other tools that use standard clinical parameters such as age, clinical or pathologic stage, grade, percent of cancer on biopsy cores, and PSA or its derivatives to predict various clinical and pathologic outcomes.

Recent studies have begun to examine a different approach by adding both cellular and biologic features to the clinical and pathologic information just noted. This approach has been called "systems pathology."

Aureon Laboratories offered 2 pathology tests called the Prostate Px+™‡ test and the Post-Op Px™‡ test (formerly called Prostate Px). Prostate Px+ was described as useful at diagnosis to patients considering surgery (radical prostatectomy) or other treatment options by providing physicians with objective information regarding the probability of disease progression. Post-Op Px estimated risk of PSA recurrence and disease progression after surgery. In October 2011, the company ceased operations and the tests are no longer offered.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Iris International offers the NADiA®‡ ProsVue™‡ test, which received U.S. FDA 510(k) clearance in 2011.The NADiA ProsVue test evaluates risk of prostate cancer recurrence after radical prostatectomy when PSA levels are less than 0.1 ng/mL. The NADiA immunoassay, polymerase chain reaction test is used to determine PSA levels on 3 serum samples taken between 6 weeks and 20 months after radical prostatectomy. The PSA data are entered into the ProsVue software to ensure appropriate serum sample use and calculation of assay results and to determine the rate of PSA change, the PSA slope.

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Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Assessment of a diagnostic test, including tests that are used to predict clinical risk, typically focuses on 3 parameters: (1) technical performance; (2) diagnostic performance (sensitivity, specificity, and positive and negative predictive value) in appropriate populations of patients; and (3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility).

Technical performance for such testing may compare test measurements with a criterion standard and may also compare results taken on different occasions (test-retest).

Diagnostic performance is evaluated by the ability of a test to accurately predict the clinical outcome. The sensitivity of a test is the ability to detect a disease (determine an outcome) when the condition is present (true positive), while the specificity is the ability to detect the absence of a disease or outcome when the disease is not present (true negative).

A key aspect in evaluating clinical test performance is evidence related to improvement of clinical outcomes with use of this testing, that is, evidence that assesses the link between use of a test to changes in health outcomes (clinical utility). In a clinical area such as prostate cancer in which multiple tools to predict risk already exist, a new test must demonstrate that any improvement in predictive accuracy results in meaningful changes in therapy and leads to improved outcomes. In many cases, comparative trials are needed to demonstrate the impact of testing on net health outcome.

Literature Review

In 2008, Donovan et al reported on use of a systems pathology tool through integration of clinicopathologic data with image analysis and quantitative immunofluorescence of prostate cancer tissue. In this study, an algorithm for postoperative risk was derived using a cohort of 758 patients with clinically localized or locally advanced prostate cancer who had tissue available for analysis and for whom outcomes were known. This cohort was assembled from 1 institution; the patients were initially treated between 1985 and 2003. Samples were identified for 971 patients, but the cohort was reduced to 881 because some patients received treatment before prostatectomy and treatment before clinical failure. An additional 123 patients were excluded because of missing data elements, including missing outcome information. The derived model predicted distant metastasis and/or androgen-independent recurrence. The model was derived using 40 potential variables. The outcome was clinical failure; clinical failure was defined as unequivocal radiographic or pathologic evidence of metastasis, increasing PSA in a castrate state, or death related to prostate cancer.

The model was derived using a training set of 373 patients with 33 (8.8%) clinical failure events (24 positive bone scans and 9 patients with increasing PSA levels). The model included androgen receptor levels,

dominant prostatectomy Gleason grade, lymph node involvement, and 3 quantitative characteristics from hematoxylin and eosin (H&E) staining of prostate tissue. The model had a sensitivity of 90% and specificity of 91% for predicting clinical failure within 5 years after prostatectomy. The model was then validated on an independent cohort of 385 patients with 29 (7.5%) clinical failure events (22 positive bone scans, 7 with increasing PSA levels). This gave a sensitivity of 84% and specificity of 85%. High levels of androgen receptor predicted shorter time to castrate PSA increase after androgen deprivation therapy. The authors concluded that the integration of clinicopathologic variables with imaging and biomarker data (systems pathology) resulted in a highly accurate tool for predicting clinical failure within 5 years after prostatectomy. They also noted support for a role for androgen-receptor signaling in clinical progression and duration of response to androgen-deprivation therapy.

In a subsequent article from 2009, Donovan et al reported on derivation of another system's pathology model to predict risk in prostate cancer based on preoperative assessment, including biopsy results. This publication reported on efforts to develop a patient-specific, biology-driven tool to predict outcome at diagnosis. The study also investigated whether biopsy androgen receptor levels predict a durable response to therapy after secondary treatment. The authors evaluated paraffin-embedded prostate needle biopsy tissue from 1027 patients with T1c-T3 prostate cancer treated with surgery between 1989 and 2003 and followed a median of 8 years. Information was initially compiled on 1487 patients from 6 institutions. Four-hundred sixty patients were excluded from analysis because of incomplete or missing information. Clinical failure was determined as noted in the study previously summarized. Modeling again began with 40 candidate variables. In the training set of 686 patients, 87 (12.7%) had clinical failure (9 with a positive bone scan and 78 with increasing PSA in a castrate state).

A total of 219 (32%) of these patients received standard androgen ablation with or without salvage radiotherapy. These treatments were done at the discretion of the treating physician for the cohort of patients in this analysis. Using clinical failure within 8 years as the outcome, the model had a sensitivity of 78% and specificity of 69% in the derivation set. The 6 variables in this model were as follows: preoperative PSA, dominant biopsy Gleason grade, biopsy Gleason score, and 3 systems pathology variables (androgen receptor, distance between epithelial tumor cells, tumor epithelial cell area). Patients from another (the fifth) institution were used for the validation set. In the validation set of 341 patients, the sensitivity was 76% and specificity 64%. There were 44 clinical failures (4 with positive bone scan, 40 with increasing PSA in a castrate state). This study also found that increased androgen receptor in biopsy tumor cells predicted resistance to therapy. The authors concluded that the additional systems pathology data add to the value of prediction rules used to assess outcome at diagnosis. The authors also comment that the nature of this study has the potential for bias.

Some of the investigators from these two studies were also involved in an earlier report from Memorial Sloan-Kettering on using this approach to predict clinical failure (as measured by PSA recurrence) following radical prostatectomy. This study involved a training set of 323 patients.

Similarly, Eggener et al from the University of Chicago described development of 2 systems pathology models to determine which patients undergoing radical prostatectomy are likely to manifest systemic disease. They found their models to be accurate and commented that use of the novel markers may enhance the accuracy of the systems pathology approach.

Veltri et al from Johns Hopkins reported on use of nuclear morphometric signatures such as nuclear size, shape, DNA content, and chromatin texture in predicting PSA recurrence. This model was found to have an area under the receiver operating characteristic curve of 0.80. The authors concluded that PSA recurrence is more accurately predicted using these markers compared with routine pathology information alone.

In an editorial accompanying the 2008 article by Donovan et al, Klein et al raise a number of questions. A major question raised is whether the differences with these new models have sufficient clinical relevance to justify the extra effort, expense, and expertise needed for the systems pathology approach. He comments that additional studies are needed to understand the incremental value of this new information.

The article by Donovan et al also comments that they believe this approach will allow the development of more informed and appropriate treatment plans, including the potential for early decisions about androgen deprivation therapy, radiotherapy, and/or chemotherapy in a subset of patients.

In 2010, Donovan et al investigated whether clinical variables before treatment and tumor specimen characteristics from patients with castrate-resistant metastatic prostate cancer can be used to predict time to prostate cancer–specific mortality and overall survival. H&E slides, paraffin blocks, and outcome data from 104 castrate patients with metastatic prostate cancer were independently reviewed. Pathology samples were from prostatectomy specimens (n=43) and prostate needle biopsies (n=61). Patients included in the study had local and advanced disease (T1-T4), had been managed with radiotherapy or primary hormonal therapy, 47% had PSA level 20 ng/mL or higher, and 52% had a Gleason sum of greater than 7 at the time of diagnosis. H&E morphometry and quantitative immunofluorescence assays for cytokeratin-18 (epithelial cells), 4',6-diamidino-2-phenylindole (nuclei), p63/high molecular weight keratin (basal cells), androgen receptors, and α-methyl CoA-racemase were performed. Immunofluorescence images were acquired with spectral imaging software and processed for quantification with specific algorithms. Median follow-up was 12 years from diagnosis. Of the 104 patients, 66 had evaluable immunofluorescence features. PSA level was the only clinical variable associated with outcome. The amount of androgen receptors present within tumor nuclei correlated with a greater risk of a shorter time to prostate cancer specific mortality ($p<0.05$). No H&E features correlated with mortality. The authors concluded that, using systems pathology, they were able to identify and characterize a population of cells that expressed very high levels of androgen receptors that predict a more aggressive phenotype of prostate cancer.

Two studies published by Donovan et al in 2012 both used the same sample of postoperative tissue specimens described in the 2008 article by Donovan et al. One compared the Post-Op Px algorithm with 2 other nomograms for predicting PSA recurrence and clinical failure (PSA rise, bone metastasis, or prostate cancer–related death). Data came from 373 patients included in the 2008 training set. The concordance

index was used as a measure of classification accuracy. Regarding PSA recurrence, the Px algorithm was more accurate (0.76) than the D'Amico nomogram (0.70) and the Kattan nomogram (0.75). Similarly, the Px model was more accurate for predicting clinical failure (0.84) than the D'Amico nomogram (0.73) and the Kattan nomogram (0.79). The other study used specimens from transurethral resection of the prostate in a postoperative model for predicting prostate cancer specific survival and disease progression. A training set consisted of 256 patients and a validation set included 269 patients. Performance of the training set was a concordance index of 0.79, sensitivity of 75%, and specificity of 86%. In the validation set, concordance index was 0.76, sensitivity was 59%, and specificity was 80%.

In 2012 Moul et al reported on the ability of the NADiA ProsVue to predict prostate cancer recurrence after radical prostatectomy. The NADiA test is a PSA immunoassay, polymerase chain reaction test designed to measure PSA levels less than 0.01ng/mL. The ProsVue software calculates the risk of prostate cancer recurrence based on the rate of PSA change or slope of the 3 sequential NADiA PSA values. To validate the NADiA ProsVue, archived serum samples were tested from 304 men with biopsy-confirmed prostate cancer who underwent radical prostatectomy. Included patients had 3 serum samples available from 3 different time points after prostatectomy. PSA levels in the first serum sample after radical prostatectomy were required to be less than 0.1ng/mL. Study patients had been treated from 1990 to 2001 and were followed for up to 17.6 years. The median NADiA PSA level was 3.1 pg/mL after prostatectomy in patients who did not have prostate cancer recurrence and 14.1 pg/mL in patients with recurrence ($p<0.001$). In the prostate cancer recurrent group, PSA levels increased in the subsequent 2 serum samples tested but changed minimally in patients without recurrence. Patients with a PSA slope of greater than 2.0 pg/mL/mo had a median disease-free survival of 4.8 years compared with 17.6 years in patients with a PSA slope of 2.0 pg/mL/mo or less ($p<0.001$). PSA slope of greater than 2.0 pg/mL/mo predicted a significantly higher risk of recurrence with a univariate hazard ratio of 18.3 (95% confidence interval [CI], 10.6 to 31.8; $p<0.001$). When the PSA slope was evaluated with the covariates of preprostatectomy PSA level, Gleason score and pathologic stage, the multivariate hazard ratio was 9.8 (95% CI, 5.4 to 17.8; $p<0.001$). Gleason score of 7 or more was the only other covariate that significantly predicted risk of recurrence with a hazard ratio of 5.4 (95% CI, 2.1 to 13.8; $p<0.001$).

A 2014 update of the 2012 Moul et al study reanalyzed the prognostic value of a ProsVue result 2.0 pg/mL/mo or less and risk as stratified by a nomogram called the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) nomogram, for a reduced risk of prostate cancer–specific survival. The authors also assessed its value for predicting clinical outcome in men who received salvage treatment for biochemical recurrence. Median overall survival for men with a ProsVue slope of 2.0 or less and greater than 2.0 pg/mL/mo was 11.0 years (95% CI, 9.4 to 12.9) and 9.2 years (95% CI, 4.9 to 11.6), respectively. ProsVue univariate hazard ratio for prostate cancer–specific survival was 20.6 (95% CI, 6.8 to 62.7), with $p<0.000$ for a ProsVue result greater than 2.0 pg/mL/mo versus a result 2.0 pg/mL/mo or less. ProsVue multivariate hazard ratio adjusted by CAPRA-S nomogram was 16.7 (95% CI, 4.7 to 58.6; $p<0.000$). Based on 18 events, salvage treatment for biochemical recurrence did not significantly reduce the hazard of clinical recurrence or prostate cancer–specific mortality.

In 2014, Moul et al reported on the prospective enrollment of men treated by radical prostatectomy into a multicenter trial to assess the clinical utility of ProsVue PSA slope results. At postsurgical follow-up, men were stratified into low-, intermediate-, or high-risk groups for cancer recurrence based on clinicopathologic findings and other findings. Three serial serum samples for ProsVue testing were collected. Investigators recorded whether their initial treatment plan was changed after the ProsVue result was reported. Of 225 men, 128 (57%) were stratified into intermediate- and high-risk groups. Investigators reported that they would have referred 41 of 128 (32%) of these men for secondary treatment but that after the ProsVue result was reported, they referred 15 of 128 (12%) of these men.

It is unknown whether the NADiA ProsVue after radical prostatectomy results in improved health outcomes, and there is no evidence to demonstrate incremental predictive value over other variables such as Gleason score or independent PSA levels.

Summary of Evidence
Systems pathology, an approach that combines cellular and biologic features to standard clinical parameters such as age, clinical or pathologic stage, grade, percent of cancer on biopsy cores, and PSA or its derivatives, is proposed as a way to estimate the probability of disease progression or recurrence, either before or after prostatectomy.

Studies are needed to determine which patients may benefit from this testing, as well as to determine when in the course of diagnosis and treatment the systems pathology assessment should be performed. There also should be further discussion about which outcomes are the best to be used in developing models; there can be substantial differences in models that predict PSA recurrence from those that predict metastatic disease and those that predict death. In addition, models may be needed that evaluate risk following treatments other than radical prostatectomy. The value of using the systems pathology approach to determine risk is not known based on currently available studies. Thus, the impact on clinical outcomes is not known and the clinical utility of this testing is not known. Therefore, this testing is considered investigational.

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Policy History

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02/03/2011	Medical Policy Committee review
02/16/2011	Medical Policy Implementation Committee approval. New policy.
02/02/2012	Medical Policy Committee review
02/15/2012	Medical Policy Implementation Committee approval. “Uses” changed to “include” to improve the clarity of the investigational statement. Coverage eligibility unchanged.
02/07/2013	Medical Policy Committee review
02/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Title changed to Systems Pathology in Prostate Cancer.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. No change to coverage.
12/03/2018	Coding update

Next Scheduled Review Date: 01/2019

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	88313, 88323, 88346, 88350, 88399
HCPCS	No codes
ICD-10 Diagnosis	C61, R97.21, Z85.46

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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