Systems Pathology in Prostate Cancer

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Last Review: 8/2014  
Origination: 8/2010  
Next Review: 8/2015

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for systems pathology for predicting risk recurrence in prostate cancer. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Use of tests utilizing systems pathology that include cellular and biologic features of a tumor is considered investigational, including use in predicting risk of recurrence in patients with prostate cancer.

Considerations
There is no specific CPT code for this test.

Description of Procedure or Service
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 prostate-specific antigen or its derivatives, is proposed as a way to estimate the probability of disease progression, either prior to or following prostatectomy.

Background
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. (1)

Recent studies have begun to study a different approach by adding both cellular and biologic features to the clinical and pathological information noted above. 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.
Iris International offers the NADiA® ProsVue™ test, which received U.S. Food and Drug Administration 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.

Rationale

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

The policy was created with a literature review using MEDLINE through February 2010 and updated through February 20, 2014. (Note: The linkage between these publications and the commercially available tests is uncertain. Aspects of the Prostate Px+ test seem related to the 2009 Donovan et al article; while Post-Op Px seems more related to the 2008 Donovan et al article (both of which are discussed next.) Data related to these 2 tests may also be part of information that has been presented at meetings and is available only as an abstract.

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. (2) 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 prostate-specific antigen (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 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 and 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.(3) 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.(3) 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 and 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. In an attempt to reduce this bias and to perform a more robust validation study, they are investigating access to samples from randomized controlled trials.

Some of the investigators from these 2 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.(4) 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.(5) 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.(6) 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(7) accompanying the 2008 article by Donovan et al,(2) 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
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, radiation therapy, 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. Hematoxylin and eosin (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). It is unknown whether the NADiA ProsVue would alter clinical management after radical prostatectomy, and there is no evidence to demonstrate incremental predictive value over other variables such as Gleason score or independent PSA levels.

Summary

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 prostate-specific antigen (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.

Medicare National Coverage

No national coverage determination (NCD) was identified. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

10. Donovan MJ, Khan FM, Powell D et al. Postoperative systems models more accurately predict risk of significant disease progression than standard risk groups and a 10-year postoperative


Billing Coding/Physician Documentation Information
There is no specific CPT code for this test.
The Prostate Px+ test is most likely reported as follows:
- 88313 (2 units) – Special stains; Group II, all other (e.g., iron, trichrome), except immunocytochemistry and immunoperoxidase stains, including interpretation and report, each
- 88323 (1 unit) – Consultation and report on referred material requiring preparation of slides
- 88347 (8 units) – Immunofluorescent study, each antibody; indirect method
- 88399 (1 unit) – Unlisted, surgical pathology procedure

The Post-op Px test is most likely reported as follows:
- 88313 (1 units) – Special stains; Group II, all other (e.g., iron, trichrome), except immunocytochemistry and immunoperoxidase stains, including interpretation and report, each
- 88323 (1 unit) – Consultation and report on referred material requiring preparation of slides
- 88347 (5 units) – Immunofluorescent study, each antibody; indirect method
- 88399 (1 unit) – Unlisted, surgical pathology procedure

Additional Policy Key Words
N/A

Policy Implementation/Update Information
8/1/10 New policy; considered investigational.
8/1/11 No changes to intent of policy statement (“uses” changed to “include” to improve clarity).
8/1/12 No policy statement changes.
8/1/13 No policy statement changes.
8/1/14 Removed "for predicting risk of recurrence" from policy title.

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