Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer

Medical Policy

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Description

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, 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 two 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 gained U.S. Food and Drug Administration (FDA) 510(k) clearance in late 2011 for its Nadia ProsVue test, which combines immunoassay and real-time polymerase chain reaction (PCR) methodologies to determine the risk for recurrence of prostate cancer for 8 years after prostatectomy.

Policy

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.

Policy Guidelines

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

The company states that the unlisted code is used to represent “the complex integrated data capture, image analysis and advanced supervised statistical modeling technologies necessary to perform this test.”

It is possible that code 99090, analysis of clinical data stored in computers (e.g., electrocardiograms [ECGs], blood pressures, hematologic data), may be used instead of the unlisted code.
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 gold 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 March 2012. (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. paper; while Post-Op Px seems more related to the 2008 Donovan et al. paper (both of which are discussed next). Data related to these two tests may also be part of information that has been presented at meetings and is available only as an abstract.

In 2008, Donovan and colleagues 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 one 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 and colleagues 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 1,027 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 1,487 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 summarized above. 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 ablative therapy. (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, and 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, clinical trials (RCTs).

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 and colleagues from the University of Chicago described development of two 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 and colleagues 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 (ROC) 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 approach. He comments that additional studies are needed to understand the incremental value of this new information.

The paper 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. (8) 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). The 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.
Summary

As demonstrated by the data, the studies described above do not address the clinical utility of this testing. That is, currently it is not known whether use of these models that use systems pathology will result in changes in care that lead to improved patient outcomes. Additional data are needed to answer this important question.

In addition, 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.

References:


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