Medical Policy

Subject:	Systems Pathology Testing for Prostate Cancer		
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Description/Scope

This document addresses the use of the systems pathology method for individuals with prostate cancer. Systems pathology is a novel computer-based diagnostic tool combining data using the cellular and biologic features of a pathological specimen, including computerized image analysis and quantitative immunofluorescence, in addition to clinical information, such as age and clinical or pathological stage, with the results of other lab tests to produce an estimate of the risk of disease progression or recurrence.

Position Statement

Investigational and Not Medically Necessary:

Use of the laboratory tests using systems pathology methodology for individuals with prostate cancer is considered **investigational and not medically necessary.**

Rationale

The available information regarding the use of systems pathology methods in the risk estimation of disease recurrence and the impact of the resultant data is very limited. At this time, there are only a limited number of peer-reviewed published articles.

Donovan and colleagues (2008) reported on use of a systems pathology tool involving the 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 individuals with clinically localized or locally advanced prostate cancer who had tissue available for analysis and for whom outcomes were known. Samples were initially identified for 971 subjects, but the cohort was reduced to 881 because some individuals received treatment before prostatectomy or clinical failure and an additional 123 individuals were excluded because of missing data elements, including missing outcome information. The algorithm was designed to predict distant metastasis and/or androgen-independent recurrence using 40 potential variables. The outcome of 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 sub-set of 373 subjects with 33 (8.8%) clinical failure events (24 positive bone scans and 9 subjects with increasing PSA levels). The algorithm also included androgen receptor levels, dominant prostatectomy Gleason grade, lymph node involvement, and three quantitative characteristics from hematoxylin and eosin staining of prostate tissue. The algorithm had a sensitivity of 90%, and specificity of 91% for predicting clinical failure within 5 years after prostatectomy. This algorithm was then validated on an independent cohort of 385 subjects with 29 (7.5%) clinical failure events (22 positive bone

scans and 7 with increasing PSA levels) with 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 another article published in 2009, Donovan reported on derivation of another systems 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 and 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 individuals with T1c-T3 prostate cancer treated with surgery and followed for a median of 8 years. Information was initially compiled on 1487 individuals from six institutions. A total of 460 subjects 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 subset of 686 subjects, 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 received standard androgen ablation with or without salvage radiotherapy. These treatments were done at the discretion of the treating physician for the cohort of subjects 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 six variables in this model were as follows: preoperative PSA, dominant biopsy Gleason Grade, biopsy Gleason Score, and three systems pathology variables (androgen receptor, distance between epithelial tumor cells, and tumor epithelial cell area). In the validation set of 341 subjects, 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 adds 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.

Two studies were published by Donovan and colleagues in 2012. Both used the same sample of postoperative tissue specimens described in the 2008 paper by Donovan. The first paper involved data from 373 subjects and compared the Post-op Px algorithm with two other nomograms for predicting PSA recurrence and clinical failure (PSA rise, bone metastasis or prostate cancer-related death) (2012a). 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 second study used specimens from transurethral resection of the prostate (TURP) in a postoperative model for predicting prostate cancer-specific survival and disease progression (2012b). A training set consisted of 256 subjects and a validation set included 269 subjects. Performance of the training set was a concordance interval (CI) of 0.79, sensitivity of 75%, and specificity of 86%. In the validation set, the concordance index was 0.76, sensitivity was 59% and specificity was 80%.

Some of the investigators from these 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 (Cordon-Cardo, 2007). This study involved a training set of 323 individuals with prostate cancer. Similarly, Eggener and colleagues from the University of Chicago described development of two systems pathology models to determine which individuals undergoing radical prostatectomy are likely to manifest systemic disease (2009). They found their models to be accurate and commented that use of the novel markers may enhance the accuracy of the systems pathology approach.

In an editorial accompanying the 2008 article by Donovan, Klein raises a number of important questions regarding systems pathology tests including 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.

In a small study of 52 subjects, Graversen and colleagues compared the percent agreement between the endpoints of two separate systems pathology-based tests for prostate cancer, the Px and Px+ tests (2012). The Px+ test endpoints are disease progression (Px+DP), and favorable pathology (Px+FP). The endpoints for the Px test are PSA recurrence (PxPSAR) and disease progression (PxDP). These data points were compared to Gleason scores. The results demonstrated that the percent agreement between Px+DP and PxDP, Px+DP and PSAR, Px+FP and PxDP, and Px+FP and PSAR were 77%, 87%, 77%, and 79%, respectively. The Px+FP classification was also compared with postprostatectomy pathology results. The percent agreement between a Px+FP classification of high, dominant Gleason score ≤ 3, Gleason sum ≤ 6, and ECE were reported to be 71.7%, 37.7%, and 60%, respectively. The authors stated that the percent agreement between Px+ and Px testing endpoints for individuals undergoing radical prostatectomy was very good. They also stated that there was a direct correlation between most Px+ and Px endpoints. However, the Px+FP classification and Gleason sum demonstrated a poor agreement. Overall, the authors said that results demonstrated that the two independent systems-based models for prostate cancer provide strong cross-model agreement and demonstrate significant correlation with clinical endpoints but conclude by saying that, "Further testing with a large cohort including long-term studies is warranted."

Moul published a study investigating the ability of the NADiA® ProsVue™ test to predict prostate cancer recurrence after radical prostatectomy (2012). The NADiA ProsVue test was first validated using archived serum PSA samples from 304 subjects with biopsy-confirmed prostate cancer who underwent radical prostatectomy. Of this population, 64 subjects had clinical recurrence and 240 subjects were controls. Included subjects had three serum PSA samples available from three different time points after prostatectomy. Study subjects were initially treated between 1990 and 2001. Follow-up duration was 17.6 years. The authors reported that the median NADiA detected PSA level was 3.1 pg/mL after prostatectomy in subjects who did not have prostate cancer recurrence and 14.1 pg/mL in subjects with recurrence ($p<0.001$). In the recurrent group, PSA levels increased in the subsequent two serum samples but changed minimally in subjects without recurrence. Subjects with a PSA slope of greater than 2.0 pg/ml/mo had a median disease-free survival of 4.8 years compared to 17.6 years in subjects 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 (HR) of 18.3 (95% CI, 10.6 to 31.8; $p<0.001$). When the PSA slope was evaluated with the covariates of pre-prostatectomy 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.

An update of the study described above was published in 2014 (Moul, 2014a). This study reanalyzed the prognostic value of a ProsVue result of 2.0 pg/mL/mo or less. The authors reported that the median overall survival for men with a ProsVue slope of ≤ 2.0 pg/mL/mo was 11.0 years and > 2.0 pg/ml/mo was 9.2 years. The Area Under the Curve (AUC) of ProsVue for discriminating between men who did and did not develop clinical recurrence was 0.906, with a positive predictive value (PPV) of 78.0% and a negative predictive value (NPV) of 92.7% at the 2.0 pg/ml/mo slope cut point. The AUC for discriminating between men who did and did not die of prostate cancer was 0.902, with a PPV of 23.7% and NPV of 98.4% at the same slope cut point. In a univariate Cox regression analysis, a ProsVue result of > 2.0 pg/ml/mo was the most powerful risk factor for clinical outcomes, and hazard ratios (HRs) for clinical recurrent and prostate cancer-specific mortality were 18.5 and 20.5 respectively ($p<0.0001$ for both). The use of salvage treatment for biochemical recurrence was also analyzed, and was not found to significantly reduce the hazard of clinical recurrence or prostate cancer-specific mortality.

Another study by the same group prospectively enrolled 225 subjects treated by radical prostatectomy (Moul, 2014b). Subjects were stratified into low-, intermediate- or high-risk groups at postsurgical follow-up visits based on clinicopathological findings and other factors. The authors serially collected three serum samples for ProsVue testing and recorded whether or not the initial treatment plan was changed based on test findings. In the study population, 128 subjects (56.9%) were stratified into intermediate- and high-risk groups. The investigators reported that they would have referred 41/128 (32.0%) at-risk subjects for secondary treatment. However, after results were known, they referred only 15/128 (11.7%) subjects. The difference in proportions (-20.3%, 95% CI, -29.9 to -10.3%) is significant ($p<0.0001$). The odds of a referral was significantly reduced after results were reported (odds ratio 0.28, 95% CI, 0.15-0.54; $p<0.0001$). While the reported results of this study indicate that knowledge of a ProsVue result had an impact on the final treatment plan, no data are presented to demonstrate that this impact resulted in beneficial clinical outcomes in these individuals who had altered treatment plans.

Currently available studies have not established the clinical utility of this type of testing. That is, it is not known whether use of system pathology models would result in medical or surgical management changes leading to improved health outcomes for individuals with prostate cancer. Additional studies are also needed to determine which individuals may benefit from this type of testing, when in the course of diagnosis and treatment the systems pathology testing should be performed, and what outcomes should be used in developing models (for example, metastatic disease, death from prostate cancer). Finally, algorithms may be needed that consider risks following treatments other than radical prostatectomy.

Background/Overview

Predicting the risk of prostate cancer progression or recurrence is difficult in individuals. The current standard of care uses risk models involving the use of family and individual history and clinical data. A new type of risk estimation tool, using a "systems pathology" approach, has been developed. In addition to the data used in traditional risk estimation tools, tests using the systems pathology method add data regarding molecular and cellular biology from tumor samples, as well as advanced image analysis to identify and measure clinical, micro-

anatomical, and molecular features to aid in predicting specific individual clinical outcomes. Some systems pathology tests also use proprietary computer-based and mathematical modeling algorithms to calculate risk estimation data.

Several systems pathology tests have been made commercially available, including the Prostate Px+ test and the Post-Op Px test (formerly called Prostate Px) (Aureon Biosciences, Inc.; Yonkers, NY), and the NADiA ProsVue test (Iris Diagnostics; Chatsworth, CA). The NADiA test is a PSA immunoassay, polymerase chain reaction test designed to measure PSA levels less than 0.01 ng/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. In October 2011, Aureon Biosciences, the company that produces the Prostate Px+ and the Post-Op Px tests, ceased operations, thus these tests are no longer available.

In 2017, the American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) published a joint clinical guideline for the treatment of clinically localized prostate cancer (Sanda, 2017). There is no mention of systems pathology testing in this document.

Definitions

Systems pathology: A novel approach to estimate the risk of disease progression. Tests using the systems pathology method add data regarding molecular and cellular biology from tumor samples, as well as advanced image analysis to identify and measure clinical, micro-anatomical, and molecular features which may aid in predicting specific individual clinical outcomes. Some systems pathology tests also use proprietary computer-based and mathematical modeling algorithms to calculate risk estimate data.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
88399	Unlisted surgical pathology procedure [when specified as systems pathology test to predict prostate cancer progression or recurrence]
0376U	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate ArteraAI Prostate Test, Artera Inc©, Artera Inc©

ICD-10 Diagnosis

C61	Malignant neoplasm of prostate
D07.5	Carcinoma in situ of prostate
Z85.46	Personal history of malignant neoplasm of prostate

References

Peer Reviewed Publications:

1. Cordon-Cardo C, Kotsianti A, Verbel DA, et al. Improved prediction of prostate cancer recurrence through systems pathology. J Clin Invest. 2007; 117(7):1876-1883.
2. Donovan MJ, Hamann S, Clayton M, et al. Systems pathology approach for the prediction of prostate cancer progression after radical prostatectomy. J Clin Oncol. 2008; 26(24):3923-3929.
3. Donovan MJ, Khan FM, Bayer-Zubek V, et al. A systems-based modelling approach using transurethral resection of the prostate (TURP) specimens yielded incremental prognostic significance to Gleason when predicting long-term outcome in men with localized prostate cancer. BJU Int. 2012b; 109(2):207-213.
4. Donovan MJ, Khan FM, Fernandez G, et al. Personalized prediction of tumor response and cancer progression on prostate needle biopsy. J Urol. 2009; 182(1):125-132.
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6. Eggener SE, Vickers AJ, Serio AM, et al. Comparison of models to predict clinical failure after radical prostatectomy. Cancer. 2009; 115(2):303-310.
7. Graversen JA, Suh LK, Mues AC, et al. Independent diagnostic and post-treatment prognostic models for prostate cancer demonstrate significant correlation with disease progression end points. J Endourol. 2012; 26(5):451-456.
8. Klein EA, Stephenson AJ, Raghavan D, Dreicer R. Systems pathology and predicting outcome after radical prostatectomy. J Clin Oncol. 2008; 26(24):3916-3917.
9. Moul JW, Chen DY, Trabulsi EJ, et al. Impact of NADiA ProsVue PSA slope on secondary treatment decisions after radical prostatectomy. Prostate Cancer Prostatic Dis. 2014b; 17(3):280-285.
10. Moul JW, Lilja H, Semmes OJ, et al. NADiA ProsVue prostate-specific antigen slope is an independent prognostic marker for identifying men at reduced risk of clinical recurrence of prostate cancer after radical prostatectomy. Urology. 2012; 80(6):1319-1325.
11. Moul JW, Sarno MJ, McDermed JE, et al. NADiA ProsVue prostate-specific antigen slope, CAPRA-S, and prostate cancer--specific survival after radical prostatectomy. Urology. 2014a; 84(6):1427-1432.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Sanda MG, Chen RC, Crispino T, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. 2022. Available at: http://www.auanet.org//guidelines-and-quality/guidelines/clinically-localized-prostate-cancer-aua/astro-guideline-2022. Accessed on September 22, 2022.

Websites for Additional Information

1. American Cancer Society (ACS). Available at: http://www.cancer.org. Accessed on September 22, 2022.
2. National Cancer Institute (NCI) – Prostate cancer treatment. Last modified February 2, 2022. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/prostate/healthprofessional. Accessed on September 22, 2022.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	03/29/2023	Updated Coding section with 04/01/2023 CPT changes; added 0376U.
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Reviewed	11/05/2020	MPTAC review.
Reviewed	11/07/2019	MPTAC review.
Reviewed	11/08/2018	MPTAC review.
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Reviewed	11/02/2017	MPTAC review.
Reviewed	11/01/2017	Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated References section.
Reviewed	11/03/2016	MPTAC review.
Reviewed	11/02/2016	Hematology/Oncology Subcommittee review. Updated References section.
Reviewed	11/05/2015	MPTAC review.
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Reviewed	11/13/2014	MPTAC review.
Reviewed	11/12/2014	Hematology/Oncology Subcommittee review. Updated Rationale and Reference sections.
Reviewed	11/14/2013	MPTAC review.

Reviewed	11/13/2013	Hematology/Oncology Subcommittee review. Updated Rationale and Reference sections.
Reviewed	11/08/2012	MPTAC review.
Reviewed	11/07/2012	Hematology/Oncology Subcommittee review. Updated Rationale and Reference sections.
Reviewed	11/17/2011	MPTAC review.
Reviewed	11/16/2011	Hematology/Oncology Subcommittee review.
New	02/17/2011	MPTAC review. Initial document development.