BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

# Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer - Prostate Px Test

**Policy #** 00286
Original Effective Date: 02/16/2011
Current Effective Date: 01/15/2014

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

**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

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.

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 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 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.

## Rationale/Source

Assessment of a diagnostic test, including tests that are used to predict clinical risk, typically focuses on three parameters: 1) its 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).

Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer - Prostate Px Test

Policy # 00286
Original Effective Date: 02/16/2011
Current Effective Date: 01/15/2014

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 a prostate cancer where 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 linkage between these publications and the commercially available tests is uncertain. Aspects of the Prostate Px+ test seem related to the 2009 Donovan paper; while Post-Op Px seems more related to the 2008 Donovan paper. Data relating 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. 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 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 three 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 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 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. 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 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 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 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 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.

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 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. 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, deoxyribonucleic acid (DNA) content, and chromatin texture in predicting PSA recurrence. 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 accompanying the 2008 article by Donovan et al. Klein raises 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 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 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. Prostate-specific antigen 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 paper by Donovan et al. One compared the Postop 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 (CI) 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 (TURP) 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 CI of 0.79, sensitivity of 75%, and specificity of 86%. In the validation set, CI was 0.76, sensitivity was 59% and specificity was 80%.

Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer - Prostate Px Test

Policy # 00286
Original Effective Date: 02/16/2011
Current Effective Date: 01/15/2014

**Summary**
Data on the use of systems pathology for predicting risk of recurrence in prostate cancer do not address the clinical utility of this testing. Therefore, it is not known whether use of these models 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.

## References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer", 2.04.64, 3:2013.
2. Shariat SF, Karakiewicz PI, Margulis V et al. Inventory of prostate cancer predictive tools. Curr Opin Urol 2008; 18(3):279-96.
3. 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):3923-9.
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):125-32.
5. Cordon-Cardo C, Kotsianti A, Verbel DA et al. Improved prediction of prostate cancer recurrence through systems pathology. J Clin Invest 2007; 117(7):1876-83.
6. Eggener SE, Vickers AJ, Serio AM et al. Comparison of models to predict clinical failure after radical prostatectomy. Cancer 2009; 115(2):303-10.
7. Veltri RW, Miller MC, Isharwal S et al. Prediction of prostate-specific antigen recurrence in men with long-term follow-up postprostatectomy using quantitative nuclear morphometry. Cancer Epidemiol Biomarkers Prev 2008; 17(1):102-10.
8. Klein EA, Stephenson AJ, Raghavan D et al. Systems pathology and predicting outcome after radical prostatectomy. J Clin Oncol 2008; 26(24):3916-7.
9. Donovan MJ, Osman I, Khan FM. Androgen receptor expression is associated with prostate cancer-specific survival in castrate patients with metastatic disease. BJU Int 2010; 105(4):462-7.
10. 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 2012; 109(2):207-13.
11. 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 nomogram: potential impact on the receipt of adjuvant therapy after surgery. BJU Int 2012; 109(1):40-5.

## Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician*.

Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer - Prostate Px Test

Policy # 00286
Original Effective Date: 02/16/2011
Current Effective Date: 01/15/2014

*The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

*CPT is a registered trademark of the American Medical Association.*

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, 88347, 88399 |
| HCPCS | No codes |
| ICD-9 Diagnosis | 185, V10.46 |
| ICD-9 Procedure | No codes |

## Policy History

Original Effective Date: 02/16/2011
Current Effective Date: 01/15/2014
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.
Next Scheduled Review Date: 01/2015

*****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. Food and Drug Administration (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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.