BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Systems Pathology in Prostate Cancer

Policy #: 428
Category: Medicine/Laboratory

Latest Review Date: August 2019
Policy Grade: **Effective January 28, 2016: Active Policy but no longer scheduled for regular literature reviews and updates.**

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

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 (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 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 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.

Policy:

Effective for dates of service on or after June 26, 2010:

Blue Advantage will treat the **use of tests utilizing "Systems Pathology" that include cellular and biologic features of a tumor** as a **non-covered** benefit and as **investigational,** including use in predicting risk of recurrence in patients with prostate cancer.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The policy was updated with a literature review through February 2010 and updated through November 12, 2015.

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

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 eight 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). 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 (four 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).

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 (95% CI) for prostate cancer-specific survival was 20.6 (6.8-62.7), 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 [4.7-58.6]; $p<0.000$. 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 post-surgical 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 41/128 (32%) of these men for secondary treatment but that after the ProsVue result was reported, they referred 15/128 (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
Systems pathology, an approach that combines cellular and biological 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 prior to or following 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.

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network guidelines on Prostate Cancer Early Detection and Prostate Cancer V2.2015 do not address systems pathology.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:

Prostate Cancer, Progression Prediction, Predicting Recurrence Risk, Systems Pathology, Quantitative Nuclear Morphometry, Prostate, Aureon, Post-op Px, Prostate Px, Prostate Px+, Nadia ProsVue

Approved by Governing Bodies:

Iris International offers the NADiA® ProsVue™ test which received 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 three serum samples taken between six weeks and 20 months after radical prostatectomy. The PSA data is 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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

There is no specific CPT code for this test. Various combinations of the following codes may be used to report this testing:

88313	Special stains including interpretation and report; Group II all other (e.g., iron, trichrome), except stain for microorganisms, stains for enzyme constituents, or immunocytochemistry and immunohistochemistry
88323	Consultation and report on referred material requiring preparation of slides
88346	Immunofluorescence, per specimen; initial single antibody stain procedure **(Effective 01/01/2016)**
88350	each additional single antibody stain procedure (List separately in addition to code for primary procedure) **(Effective 01/01/2016)**
88399	Unlisted, surgical pathology procedure

The company stated at the time that the unlisted code was 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.

Previous Coding:

CPT Codes:

88347	Immunofluorescent study, each antibody; indirect method **(Deleted effective 01/01/2016)74**

References:

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):1876-83.
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):3923-9.
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 2012; 109(2):207-13.
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. 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.
6. 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.
7. Eggener SE, Vickers AJ, Serio AM, et al. Comparison of models to predict clinical failure after radical prostatectomy. Cancer 2009; 115(2):303-10.
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. 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. Sep 2014;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):1319-25.
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. Dec 2014;84(6):1427-1432.
12. Shariat SF, Karakiewicz PI, Margulis V, et al. Inventory of prostate cancer predictive tools. Curr Opin Urol 2008; 18(3):279-96.
13. 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.

Policy History:

Adopted for Blue Advantage, May 2010
Available for comment May 12-June 25, 2010
Medical Policy Group, August 2011
Medical Policy Group, December 2011
Medical Policy Group, June 2012

Medical Policy Group, April 2013
Medical Policy Group, March 2014
Medical Policy Group, March 2015
Medical Policy Group, December 2015
Medical Policy Group, January 2016
Medical Policy Group, August 2019

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.