Medical Policy

Subject:	Systems Pathology and Multimodal Artificial Intelligence Testing for Cancerous and Precancerous Conditions		
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Description/Scope

This document addresses the use of the systems pathology method for individuals with prostate cancer or Barrett's esophagus, a condition that predisposes to the development of adenocarcinoma of the esophagus. Systems pathology and multimodal artificial intelligence testing are computer-based diagnostic tools combining data using the cellular and biologic features of a pathological specimen, which may include 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 estimate the risk of malignant transformation, cancer progression, recurrence, metastasis, mortality or response to drug therapy.

Note: Please see the following related documents for additional information:

- LAB.00049 Artificial Intelligence-Based Software for Prostate Cancer Detection

Position Statement

Investigational and Not Medically Necessary:

Use of laboratory tests using systems pathology and multimodal artificial intelligence methodology is considered **investigational and not medically necessary** for the testing of cancerous and precancerous lesions, including but not limited to prostate cancer and Barrett's esophagus.

Rationale

The available information regarding the use of systems pathology or multimodal artificial intelligence 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.

Prostate Cancer

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 participants, 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 participants with 33 (8.8%) clinical failure events (24 positive bone scans and 9 participants 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 participants 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 participants 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 participants, 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 participants 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 participants, 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 participants 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 participants and a validation set included 269 participants. 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 participants, 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 participants with biopsy-confirmed prostate cancer who underwent radical prostatectomy. Of this population, 64 participants had clinical recurrence and 240 participants were controls. Included participants had three serum PSA samples available from three different time points after prostatectomy. Study participants 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 participants who did not have prostate cancer recurrence and 14.1 pg/mL in participants with recurrence ($p<0.001$). In the recurrent group, PSA levels increased in the subsequent two serum samples but changed minimally in participants without recurrence. Participants 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 participants 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 participants treated by radical prostatectomy (Moul, 2014b). Participants 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 participants (56.9%) were stratified into intermediate- and high-risk groups. The investigators reported that they would have referred 41/128 (32.0%) at-risk participants for secondary treatment. However, after results were known, they referred only 15/128 (11.7%) participants. The difference in proportions (-20.3%, 95% CI, -29.9 to -10.3%) is significant (p<0.0001). The odds of a referral were 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.

Esteva et al (2022) used five phase III randomized clinical trials to demonstrate multimodal artificial intelligence can be used to predict long term outcomes in individuals with localized prostate cancer. From these clinical trials, histopathological data was available for 5654 randomized individuals. For each individual, the multimodal artificial intelligence took clinical variables and digitized histopathology slides. The image features were standardized across the trials for consistency. The authors noted that their model outperformed the NCCN model across all test outcomes, with a substantial relative improvement in the area under the curve varying from 9.2% to 14.6%. The authors concluded that further work is required to evaluate the clinical utility of this model and interpretability of features used to predict prognosis should be investigated.

The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guideline (CPG) for prostate cancer (V4.2024) discusses risk stratification. The NCCN recommends clinical tools (e.g., NCCN, STAR-CAP, CAPRA, MSKCC), gene expression testing (e.g., Decipher, Polaris, Oncotype), and germline (e.g., HRR). They are category

2A recommendations. In addition, NCCN recommends artificial intelligence (e.g., ArteraAI Prostate) as a category 2A.

Pancreatic Cancer

Cui and colleagues (2024) conducted a randomized crossover trial to compare conventional and multimodal artificial intelligence-assisted diagnosis of solid lesions in the pancreas. A retrospective dataset from 439 individuals was used to train and validate the artificial intelligence model while data from 189 individuals were used to evaluate the robustness and generalizability of the model. A total of 130 participants were recruited for the prospective crossover trial. The area under the curve of the artificial intelligence model was up to 0.976 (95% CI, 0.942-0.995) in the test dataset. The diagnostic accuracy of novice endoscopists was significantly enhanced with assistance from the artificial intelligence model. However, the authors concluded that multicenter randomized clinical trials with a larger and more diverse participant pool are needed to further assess the clinical applicability of the artificial intelligence model. In addition, this is a proprietary test that is not available in the United States.

Barrett's Esophagus

Barrett's esophagus (BE) is a condition that occurs when the cells lining the esophagus change abnormally due to damage from acid reflux. BE is a precursor to esophageal adenocarcinoma (EAC). Although the risk of progression from BE to EAC is low, early detection of those individuals who will progress to EAC is important for optimal disease management. The TissueCypher™ test (Castle Biosciences, Inc.) is an artificial intelligence-driven systems pathology test to determine an individual's risk of progression from BE to EAC (Prichard, 2015). The test characterizes molecular changes in BE tissue that precede malignant progression, with the aim of identifying individuals who will progress to EAC at a potentially treatable precancerous stage. The TissueCypher assay integrates 15 quantitative image analysis features derived from fluorescence images of 9 protein-based biomarkers, nuclear morphology, and tissue architecture to provide a risk score (0–10) that classifies individuals as low, intermediate, or high risk for progression to EAC within 5 years.

There have been several validation studies performed on the TissueCypher test. Critchley-Thorne and colleagues (2016) evaluated the test using a retrospective case-control study design. Individuals who progressed to high-grade dysplasia or EAC in ≥1 year (n=79) were matched with individuals who did not progress (n=287). Using the TissueCypher score in a 3-tier stratification to classify individuals as low, intermediate, or high risk for progression, the NPV and PPV were 98% and 26%, respectively. In other studies, the sensitivity and specificity of TissueCypher at 5 years for the 3-tiered classification system were 29-30.4% and 86-95%, respectively (Davison, 2020; Frei, 2020). Sensitivity and specificity for a 2-tiered classification system (high and low risk) in which intermediate and high risk groups were combined were 67.7% and 78.6%, respectively (Frei, 2021).

There are no prospective studies evaluating clinically relevant health outcomes in individuals assigned to use of the TissueCypher tests versus usual care.

The American College of Gastroenterology (ACG) in their guideline on the diagnosis and management of BE (2022) found that the use of biomarkers such as those in the TissueCypher test is hindered by their low sensitivity and specificity. The ACG also noted that:

> Although TissueCypher uses automated image analysis to eliminate subjectivity in interpretation, various external factors such as cell stress, DNA damage, and ongoing GERD [gastroesophageal reflux disease] might alter some, if not all, of the 15 features detected on the panel producing erroneous estimates; the same holds true for these factors in altering expression levels of p53.
>
> Given the low sensitivity and specificity of the above biomarkers, the panel could not make a recommendation for routine use of p53 IHC [immunohistochemistry] or TissueCypher for risk stratification in patients with BE undergoing surveillance.

The ACG recommended further research to better define the subset of individuals with BE who are most likely to benefit from biomarker tests such as TissueCypher. It also suggested that the use of biomarkers ultimately should impact harder endpoints such as cancer incidence or death.

Summary

Currently available studies have not established the clinical utility of these types of testing. That is, it is not known whether use of system pathology or multimodal artificial intelligence models would result in medical or surgical management changes leading to improved health outcomes for individuals with prostate cancer or Barrett's esophagus. Additional studies are also needed to determine which individuals may benefit from these types of testing, when in the course of diagnosis and treatment the systems pathology testing or multimodal artificial intelligence testing should be performed, and what outcomes should be used in developing models (for example, progression to clinically significant cancer, metastatic disease, death from cancer). Finally, algorithms may be needed that consider risks following available treatment and surveillance options.

Other Relevant Information

The only product discussed in this document that has received FDA clearance is the NADiA ProsVue test for prostate cancer. This test is indicated for use as a prognostic marker in conjunction with clinical evaluation as an aid in identifying those individuals at reduced risk for recurrence of prostate cancer during the 8 year period following prostatectomy.

Neither Centers for Medicare & Medicaid Services (CMS) National Coverage Determinations (NCDs) nor Local Coverage Determinations (LCDs) addressing systems pathology or multimodal artificial intelligence testing for cancerous or precancerous conditions were identified.

Nationally recognized clinical practice guidelines for tests addressed in this document are described above. NCCN recommends artificial intelligence (for example, ArteraAI Prostate) as a category 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate). Regarding TissueCypher, the ACG could not make a recommendation for routine use given the low sensitivity and specificity of these biomarkers.

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 type of risk estimation tool using a "systems pathology" approach was 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. Recently, another type of risk estimation tool using multimodal artificial intelligence was developed.

Several systems pathology tests for prostate cancer 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. ArteraAI Prostate Test (ArteraAI; Los Altos, CA) is a multimodal artificial intelligence biomarker test that utilizes algorithms that combines images from an individual's biopsy and clinical data to predict whether an individual will benefit from hormone therapy and calculates long-term outcomes in individuals with localized prostate cancer. In 2022, the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) published a joint clinical guideline for the treatment of clinically localized prostate cancer (Eastham, 2022). There is no mention of systems pathology or multimodal artificial intelligence testing in this document.

Barrett's esophagus is a condition in which metaplastic columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus, predisposing individuals to cancer development. Surveillance may be recommended to improve outcomes by detecting dysplasia or esophageal adenocarcinoma early enough to provide effective treatment; however, evidence supporting the benefits of surveillance is unclear. A number of potential harms may be associated with surveillance, including a decrease in quality of life due to anxiety about cancer development, risks associated with endoscopy, the risks and morbidity associated with invasive therapies used to treat lesions identified by surveillance (such as esophagectomy or radiofrequency ablation), and missed lesions despite surveillance. A number of promising molecular markers for cancer risk have been proposed as alternatives to biopsy sampling to detect dysplasia in Barrett's esophagus, including abnormalities in p53 and cyclin D1 expression, and abnormal cellular DNA content demonstrable by flow cytometry or methylation arrays. Additional evaluation of molecular markers is needed before they can be recommended for routine clinical use. One systems pathology test for Barrett's esophagus is currently available, the TissueCypher test (Castle Biosciences, Inc.), also known as TSP-9. The test characterizes molecular changes in Barret's esophagus tissue that precede malignant progression, with the aim of identifying individuals who will progress to esophageal adenocarcinoma at a potentially treatable precancerous stage. The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guideline (CPG) for esophageal and esophagogastric junction cancers (V3.2024) does not address TissueCypher or TSP-9 testing.

Definitions

Barrett's esophagus: A precancerous condition that occurs when the cells lining the esophagus change abnormally due to damage from acid reflux.

Multimodal Artificial Intelligence: An artificial intelligence that combines multiple types of data to create more accurate determinations or make predictions about real-world problems.

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 or multimodal AI test to predict malignant transformation, cancer progression, recurrence, metastasis, mortality or response to drug therapy]
0108U	Gastroenterology (Barrett's esophagus), whole slide–digital imaging, including morphometric analysis, computer-assisted quantitative immunolabeling of 9 protein biomarkers (p16, AMACR, p53, CD68, COX-2, CD45RO, HIF1a, HER-2, K20) and morphology, formalin-fixed paraffin-embedded tissue, algorithm reported as risk of progression to high-grade dysplasia or cancer TissueCypher® Barrett's Esophagus Assay, Cernostics, Cernostics
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

All diagnoses

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Government Agency, Medical Society, and Other Authoritative Publications:

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    - Esophageal and Esophagogastric Junction Cancers (V3.2024). Revised April 26, 2024.
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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

Revised	08/08/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Title to change "Prostate Cancer" to "Cancerous and Precancerous Conditions". Added precancerous lesions with Barrett's esophagus as an example to Position Statement. Revised Description/Scope, Rationale, Background/Overview, Definitions, References, Websites for Additional Information and Index sections. Revised Coding section to add CPT PLA code 0108U and remove specific diagnosis codes.
Revised	11/09/2023	MPTAC review. Updated Title and Position Statement and added "Multimodal Artificial Intelligence". Updated Rationale, Background/Overview, Definitions, References, Websites, and Index sections.
	03/29/2023	Updated Coding section with 04/01/2023 CPT changes; added 0376U.
Reviewed	11/10/2022	MPTAC review. Updated References and Websites sections.
Revised	11/11/2021	MPTAC review. Updated References and Websites section. Title changed to "Systems Pathology Testing for Prostate Cancer".
Reviewed	11/05/2020	MPTAC review.
Reviewed	11/07/2019	MPTAC review.
Reviewed	11/08/2018	MPTAC review.
Reviewed	10/31/2018	Hematology/Oncology Subcommittee review. Updated References and Websites section.
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.
Reviewed	11/04/2015	Hematology/Oncology Subcommittee review. Updated Rationale and Reference sections. Removed ICD-9 codes from Coding section.
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.