APPENDIX to Radioimmunoscintigraphy for Prostate Cancer Policy

Prior Authorization Requirements

This service (or procedure) is considered **investigational** for all instances. If you would like to submit additional information please forward to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

ProstaScint® (Cytogen Corp., Princeton, NJ) was approved by the United States Food and Drug Administration (FDA) for use as a diagnosing imaging agent in newly diagnosed patients with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation, who are at risk for pelvic lymph node metastases and in post-prostatectomy patients with a rising prostate-specific antigen (PSA) and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease (FDA, 1996).

Other monoclonal antibodies, directed at extracellular prostate-specific membrane antigen (PSMA) binding sites, are also under development.

This policy is based on a 1998 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment.

Since the prior TEC Assessment, several reports have been published that address the role of radioimmunoscintigraphy (RIS) in evaluating pelvic lymph node staging (Polascik et al., 1999; Manyak et al., 1999; Quintana & Blend, 2000; Murphy et al., 2000; Lau et al., 2001; Rosenthal et al., 2001). However, several of the authors of these reports appeared in multiple new and prior publications, and it seems possible that some of these populations overlapped with previously reported results derived from multicenter studies. Moreover, the diagnostic accuracy of RIS for

evaluating pelvic lymph nodes did not appear to be substantially improved in later reports (Rosenthal, et al., 2001).

Several of these reports used predictive modeling or cross-sectional correlation analysis to explore the value of RIS results in predicting the extent of disease in comparison to other factors such as prostate-specific antigen (PSA) level, Gleason score, and clinical stage of disease (Polascik et al., 1999; Murphy et al., 2000; Sodee et al., 2000).

These analyses suggested RIS provided additional and independent information that correlated with extent of disease; however, the conclusions of these studies were derived from relationships across populations and did not directly translate into how RIS results would actually be used to guide management in a manner that would improve net health outcome. Without an understanding of diagnostic accuracy and how results would influence management, it is not possible to model potential effects on health outcomes. Thus, none of the reports identified in the update supported the clinical effectiveness of using RIS to evaluate pelvic lymph nodes.

In terms of evaluating recurrent or residual disease, there are limited data showing that the use of RIS in this patient group can detect additional sites of disease and would result in different management decisions compared to decisions based on usual care (Kahn et al., 1998; Elgamal et al., 1998; Petronis et al., 1998; Seltzer et al., 1999; Quintana & Blend, 2000; Murphy et al., 2000; Sodee et al., 2000; Murphy et al., 2000; Rosenthal et al., 2001; Raj et al., 2002). Imaging evaluation may be useful in suspected recurrence due to rising PSA to localize recurrent tumor and to determine whether recurrent tumor is local to the prostate area, involves distant sites, or both. When residual or recurrent disease is only local, patients may undergo postoperative radiation therapy, whereas, when the recurrence includes distant sites, hormonal therapy would be considered. Distant hematogenous metastasis from prostate cancer most frequently involves bone but can infrequently involve other soft tissue sites. Bone scan is generally considered to be more sensitive than RIS for detecting bone metastases (Rosenthal et al., 2001). Positive RIS findings have been reported anecdotally in abnormalities other than prostate cancer, so biopsy confirmation of unexpected distant findings may be necessary to ensure proper patient management (Michaels et al., 1999; Khan & Caride, 2000; Scott et al., 2001).

The available studies are generally retrospective, descriptive reports of patterns of RIS uptake in patients with suspected recurrence. These studies, however, did not provide consistent verification of disease status, and thus the rate of false-positive and false-negative RIS studies was not well established. While some studies reported what percent of cases had associated changes in management, it is frequently difficult to specifically determine how RIS results affected management and to determine whether these changes resulted in an improvement in net health outcome.

A retrospective study by Raj et al., (2002) included 252 patients with biochemical failure following radical prostatectomy (PSA < 0.4 nanogram per milliliter (ng/mL)) who had RIS performed to localize recurrence. In this study, 72% of subjects had a positive scan. A localized (prostatic fossa only) uptake pattern was seen in 30.6%, regional uptake pattern (regional lymph nodes plus or minus prostatic fossa and no distant disease) in 42.8%, and distant uptake noted in 29.4%. This study did not report the proportion of subjects in whom patient management was altered by RIS findings. Only a minority of patients (< 20%) had also received a computed

tomography (CT) scan or bone scan showing positive findings, making comparisons across technologies subject to potential bias. A uniform reference standard was not applied in this study, and detailed follow-up was available for only about half of the patients (132 of 255). The study reports sensitivity and specificity in a small subset of subjects (i.e., 95 of 252 total or 38% of subjects) who had some degree of verification of disease status. Reported sensitivity was 73% and specificity was 53%. However, due to the selected nature of the small subset analysis, these estimates are subject to potential verification bias and may not be considered valid measures of expected performance.

Sodee et al., (2000) performed a retrospective analysis of 2154 patients with prostate carcinoma who received ProstaScint® scans, either before or after treatment. This study reported the rates of RIS scans in local, regional, and distant sites but it did not provide detailed verification of results. Therefore, sensitivity and specificity could not be determined. When analysis was stratified by whether primary treatment had been surgery, radiation, or hormonal therapy, RIS showed uptake limited to extrapelvic nodes in 8.5% to 15.1% of patients and uptake in both pelvic and extrapelvic nodes in 22.1% to 33.2% of patients. Relatively few patients had also undergone CT scanning (n = 146). When CT was compared with RIS, CT did not detect pelvic or extrapelvic nodes that were detected by RIS in 73% of CT cases. In contrast, in a separate study of 45 subjects, RIS did not perform as well as CT in detecting metastatic disease (Seltzer et al., 1999).

Some authors have explored technical modifications to improve diagnostic performance of RIS. Quintana and Blend (2000) have reported using RIS with a dual-isotope scanning technique using indium-111-labeled capromab pendetide in conjunction with a subtraction technique using technetium-99m-labeled red blood cells to improve detection of metastatic tumor sites. This study reported RIS found more extensive disease in 20% of subjects, “all other imaging tests were inconclusive.” However, results from this study were limited by incomplete follow-up and/or verification of disease status in only half of the subjects, which limited valid determination of RIS performance including sensitivity and specificity.

Kahn et al., (1998) reported results in 32 patients who received salvage pelvic radiation for suspected recurrence and had received RIS imaging. The authors reported RIS had 50% sensitivity, 89% specificity, 78% positive predictive value, and 70% negative predictive value for detecting patients who would develop tumor recurrence after irradiation.

Thomas and colleagues (2003) reported on the results of RIS in a case series of 30 men with recurrent prostate cancer treated with radiation therapy. This study found no correlation between the results of RIS and tumor control, as assessed by serial PSA levels. Further studies are necessary to demonstrate that long-term outcomes after radiation therapy are improved when RIS is used to select patients.

Several studies have described the use of single-photon emission computed tomography (SPECT)/RIS fused images, in which the RIS image was combined with a SPECT scan to provide better localization of the RIS results (DeWyngaert et al., 2004; Sodee et al., 2005; Wong et al., 2005). However, these studies are primarily technical in nature and do not focus on how the results of the study would be used to alter patient management.

A number of papers have focused on continuing efforts related to fused SPECT-CT images in patients with prostate cancer as an approach to improve the accuracy and clinical utility of this imaging technique (Seo et al., 2006). Bander (2006) reported on the use of second-generation antibodies that target extracellular PSMA in an attempt to improve the accuracy of this scan for detecting bone metastases, recognizing that bone is the first site of metastatic spread in many patients.

Proano et al., (2006) reported "early experience" on outcomes among a group of 44 patients with biochemical recurrence after radical prostatectomy that underwent a ProstaScint® scan immediately before salvage radiotherapy (RT). They noted an improved prognosis (mean follow-up of 22 months) in patients who had a negative pre-RT scan but also noted that this finding was not necessarily independent of pre-RT PSA level.

Nagda et al., (2007) reported on a series of 58 patients who had Prostascint® scans as part of an assessment of rising PSA after prostatectomy who were then treated with prostate bed RT. The four-year biochemical relapse-free survival (bRFS) rates for patients with negative Prostascint® scans (53%), positive in the prostate bed alone (45%), or positive elsewhere (74%) scan findings did not differ significantly ($p = 0.51$). The capromab pendetide scan status had no effect on bRFS. Those with a pre-RT PSA level of <1 ng/mL had improved bRFS ($p = 0.003$). The authors concluded the capromab pendetide scan had a low positive predictive value in patients with positive elsewhere uptake and the four-year bRFS was similar to that for those who did not exhibit positive elsewhere uptake.

Liauw et al., (2008) cited 82 patients with adenocarcinoma of the prostate who were treated with salvage RT for an elevated PSA level after prostatectomy. The median pre-RT PSA level was 0.63 ng/mL. Of the 82 patients, 47 (57%) had a pre-RT RIS ProstaScint® scan, which was used for both patient selection and target delineation. Patients with a pre-RT RIS scan had a lower preoperative PSA level ($p = 0.0240$) and shorter follow-up ($p = 0.0221$) than those without RIS. With a median follow-up of 44 months, the biochemical control rate was 56% at three years and 48% at five years. Margin status was the only factor associated with biochemical control on univariate ($p = 0.0055$) and multivariate ($p = 0.0044$) analysis. Patients who had prostate bed-only uptake on RIS ($n = 38$) did not have improved outcomes, with biochemical control rates of 51% at three years and 40% at five years. The authors concluded patients who were selected for treatment with RIS did not have better biochemical outcomes.

Two publications raised questions about the accuracy (including sensitivity and specificity) of immunoscintigraphy, co-registered with CT, in imaging localized prostate cancer within the prostate gland and in detecting seminal vesicle invasion (Mauraviev et al., 2009; Tsivian et al., 2010).

Version 1:2011 of the National Comprehensive Cancer Network Guidelines for prostate cancer noted a number of changes in the Guideline; this included removing ProstaScint® as a recommendation in the workup of patient with recurrence after prostatectomy and with a recurrence after radiation therapy. No other comments were found in these guidelines when searching for the term ProstaScint®.

Thus, the use of Prostascint® is considered investigational.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement Policy

Type	Number	Description
CPT	78800	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); limited area
	78801	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); multiple areas
	78802	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); whole body, single day imaging
	78803	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); tomographic (SPECT)
	78804	Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); whole body, requiring 2 or more days imaging
HCPC	A9507	Indium In-111 capromab pendetide, diagnostic, per study dose, up to 10 millicuries
ICD9 Procedure		
	92.16	Scan of lymphatic system
	92.18	Total body scan
	92.19	Scan of other site

Type	Number	Description
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

Definitions

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Scintimammography/Breast-Specific Gamma Imaging/Molecular Breast Imaging

Key / Related Searchable Words

N/A

References

- Bander NH. Technology insight: monoclonal antibody imaging of prostate cancer. Nat Clin Pract Urol. 2006; 3(4):216-25.
- Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 6.01.37 (February, 2011).
- Blue Cross Blue Shield Association. Technology Evaluation Center (TEC) Assessment. 1998; Tab 21.
- DeWyngaert JK, Noz ME, Ellerin B et al. Procedure for unmasking localization information from ProstaScint scans for prostate radiation therapy treatment planning. Int J Radiat Oncol Biol Phys 2004; 60(2):654-62.

- Elgamal AA, Troychak MJ, Murphy GP. ProstaScint® scan may enhance identification of prostate cancer recurrences after prostatectomy, radiation, or hormone therapy: analysis of 136 scans of 100 patients. Prostate 1998; 37(4):261-9.
- Kahn D, Williams RD, Haseman MK et al. Radioimmunoscintigraphy with In-111-labeled capromab pendetide predicts prostate cancer response to salvage radiotherapy after failed radical prostatectomy. J Clin Oncol 1998; 16(1):284-9.
- Khan A, Caride VJ. Indium-111 capromab pendetide (ProstaScint) uptake in neurofibromatosis. Urology 2000; 56(1):154.
- Lau HY, Kindrachuk G, Carter M et al. Surgical confirmation of ProstaScint® abnormalities in two patients with high-risk prostate cancer. Can J Urol 2001; 8(1):1199-1202.
- Liauw SL, Weichselbaum RR, Zagaja GP et al. Salvage radiotherapy after postprostatectomy biochemical failure: does pretreatment radioimmunoscintigraphy help select patients with locally confined disease? Int J Radiat Oncol Biol Phys 2008; 71(5):316-21.
- Manyak MJ, Hinkle GH, Olsen JO et al. Immunoscintigraphy with indium-111-capromab pendetide: evaluation before definitive therapy in patients with prostate cancer. Urology 1999; 54(6):1058-63.
- Mauraviev V, Madden FJ, Broadwater G et al. Use of 111in-capromab pendetide immunoscintigraphy to image localized prostate cancer foci within the prostate gland. J Urol 2009; 182(3):938-47.
- Michaels EK, Blend M, Quintana JC. 111 Indium-capromab pendetide unexpectedly localizes to renal cell carcinoma. J Urol 1999; 161(2):597-8.
- Murphy GP, Snow PB, Brandt J et al. Evaluation of prostate cancer patients receiving multiple staging tests, including ProstaScint® scintiscans. Prostate 2000; 42(2):145-9.
- Nagda SN, Mohideen N, Lo SS et al. Long-term follow-up of 111In-capromab pendetide (ProstaScint) scan as pretreatment assessment in patients who undergo salvage radiotherapy for rising prostate-specific antigen after radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 2007; 67(3):834-40.
- National Comprehensive Cancer Network. Prostate Cancer Clinical Practice Guideline. Version 1.2011. Retrieved March 1, 2011 from http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf .
- Petronis JD, Regan F, Lin K. Indium-111 capromab pendetide (ProstaScint) imaging to detect recurrent and metastatic prostate cancer. Clin Nucl Med 1998; 23(10):672-7.
- Polascik TJ, Manyak MJ, Haseman MK et al. Comparison of clinical staging algorithms and 111-indium-capromab pendetide immunoscintigraphy in the prediction of lymph node involvement in high risk prostate carcinoma patients. Cancer 1999; 85(7):1586-92.
- Proano JM, Sodee DB, Resnick MI et al. The impact of a negative (111)indium-capromab pendetide scan before salvage radiotherapy. J Urol 2006; 175(5):1668-72.
- Quintana JC, Blend J. The dual-isotope ProstaScint imaging procedure–clinical experience and staging results in 145 patients. Clin Nucl Med 2000; 25(1):33-40.

- Raj GV, Partin AW, Polascik TJ. Clinical utility of indium 111-capromab pendetide immunoscintigraphy in the detection of early, recurrent prostate carcinoma after radical prostatectomy. Cancer 2002; 94(4):987-96.
- Rosenthal SA, Haseman MK, Polascik TJ. Utility of capromab pendetide (ProstaScint®) imaging in the management of prostate cancer. Tech Urol 2001; 7(1):27-37.
- Scott DL, Halkar RK, Fischer A et al. False-positive 111 indium capromab pendetide scan due to benign myelolipoma. J Urol 2001; 165(3):910-1.
- Seltzer MA, Barbaric Z, Belldegrun A et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. J Urol 1999; 162(4):1322-8.
- Seo Y, Franc BL, Hawkins RA et al. Progress in SPECT/CT imaging of prostate cancer. Technol Cancer Res Treat 2006; 5(4):329-36.
- Sodee DB, Malguria N, Faulhaber P et al. Multicenter ProstaScint imaging findings in 2154 patients with prostate cancer. Urology 2000; 56(6):988-93.
- Sodee DB, Nelson AD, Faulhaber PF et al. Update on fused capromab pendetide imaging of prostate cancer. Clin Prostate Cancer 2005; 3(4):230-8.
- Thomas CT, Bradshaw PT, Pollock BH et al. Indium-11 capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy. J Clin Oncol 2003; 21(9):1715-21.
- Tsivian M, Wright T, Price M et al. 111-In-capromab pendetide imaging using hybrid-gamma camera-computer tomography technology is not reliable in detecting seminal vesicle invasion in patients with prostate cancer. Urol Oncol 2010 Feb 27 (Epub ahead of print).
- United States Food and Drug Administration. Development & Approval Process (Drugs). Capromab Pendetide Product Approval Information-Licensing Action. Retrieved December 3, 2010 from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080734.htm .
- Wong TZ, Turkington TG, Polascik TJ et al. ProstaScint (capromab pendetide) imaging using hybrid gamma camera-CT technology. AJR Am J Roentgenol 2005; 184(2):676-80.

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
2/25/1998	Adopted policy form BCBSA TEC	Medical Policy Committee

Effective Date	Action	Reason
11/5/2002	Coding Update	Administrative Change
1/7/2011	Policy revision with position change	Medical Policy Committee
4/1/2011	Policy revision with position change	Medical Policy Committee
07/01/2011	Administrative position update	Administrative review

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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