Medical Policy

6.01.37 Radioimmunoscintigraphy (Monoclonal Antibody Imaging) With Indium 111 Capromab Pendetide for Prostate Cancer

<table>
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<tr>
<th>Original Policy Date:</th>
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<td>Effective Date:</td>
<td>November 1, 2017</td>
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<tr>
<td>Section:</td>
<td>6.0 Radiology</td>
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Policy Statement

Radioimmunoscintigraphy using indium 111 capromab pendetide (ProstaScint®) is considered **investigational** for the evaluation and management of individuals with prostate cancer.

Policy Guidelines

• N/A

Description

Radioimmunoscintigraphy (RIS) involves the administration of radiolabeled monoclonal antibodies, which are directed against specific molecular targets, followed by imaging with an external gamma camera. Indium 111 capromab pendetide (ProstaScint) is a monoclonal antibody directed against a binding site on the prostate-specific membrane antigen.

Related Policies

• N/A

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)] prohibits 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.

Regulatory Status

In 1996, indium 111 capromab pendetide (ProstaScint®) (also referred to as CYT-356), which targets an intracellular binding site on prostate-specific membrane antigen, and was approved by the U.S. Food and Drug Administration through the biologics license application process 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 high-risk for pelvic lymph node metastases... [It] is also indicated ... in post-prostatectomy patients with a rising PSA [prostate-specific antigen] and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease.”¹ Other monoclonal antibodies, directed at extracellular prostate-specific membrane antigen binding sites, are also under development.
Rationale

Background
Radioimmunoscintigraphy is an imaging modality that uses radiolabeled monoclonal antibodies to target specific tissue types. Monoclonal antibodies that react with specific cellular antigens are conjugated with a radiolabeled isotope. The labeled antibody-isotope conjugate is then injected into the patient and allowed to localize to the target over a 2- to 7-day period. The patient then undergoes imaging with a nuclear medicine gamma camera, and radioisotope counts are analyzed. Imaging can be performed with planar techniques or by using single-photon emission computed tomography.

Literature Review
This review was informed by a 1998 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment.2

Radioimmunoscintigraphy (RIS) may be considered for use in a number of clinical indications. For this evidence review, we consider 2 clinical situations:

- As part of the pretreatment workup for the staging of prostate cancer. In this situation, the value of RIS is in detecting distant metastases not evident on other imaging studies, because detection of occult metastases is likely to alter treatment recommendations.
- In patients who have received curative treatment, but present with biochemical failure (i.e., a rising prostate-specific antigen [PSA]) without definite disease on standard imaging studies. In this situation, differentiating between local and distant recurrence is important because local recurrence may be treated with salvage radiotherapy, while distant recurrence is usually treated with androgen deprivation therapy.

Staging before Curative Treatment
Based on the 1998 TEC Assessment of RIS, sensitivity in detecting tumors in the pelvic lymph nodes ranged from 50% to 75% and specificity ranged from 72% to 92.6%.2 Pooled data from the studies reviewed in the TEC Assessment produced an estimated 61% positive predictive value. If positive RIS results were used to exclude a patient from receiving potentially curative therapy (i.e., radical prostatectomy), then 38% of patients might be harmed by inappropriately withholding the potentially curative treatment. A pooled negative predictive value of 73% have suggested that if RIS played a key role in determining that pelvic lymph nodes were clear of the tumor before radical prostatectomy, then 26.7% of patients with a negative RIS scan and truly positive lymph nodes might receive ineffective surgery. Also, there is debate over a potential survival benefit with prostatectomy in the setting of positive lymph nodes.3,4 Nevertheless, regarding evaluating the pelvic nodes, the positive predictive values and negative predictive values were not sufficiently high to avoid pelvic lymph node dissection when necessary to determine patient management.

Since the 1998 TEC Assessment, reports have addressed the role of RIS in evaluating pelvic lymph node staging.5-10 Some of them appear in multiple publications, and population studies may overlap results from multicenter studies. Moreover, the diagnostic accuracy of RIS for evaluating pelvic lymph nodes did not improve substantially over time.10

Additional reports have used predictive modeling or cross-sectional correlation analysis to explore the value of RIS results in predicting the extent of disease compared with other factors (e.g., PSA level, Gleason score, clinical stage of disease).7,8,11 Some of these are mentioned but are not the focus of this review.

In 2011, Reiter et al published a retrospective review of 197 patients who had both RIS and histopathology available at a single institution over a 4-month period.12 For detection of positive lymph nodes, the sensitivity of RIS was 60.0% (95% confidence interval [CI], 14.7% to 94.7%) and the specificity was 97.4% (95% CI, 92.3% to 100%). The area under the receiver operating
characteristic curve was 0.787. Increasing Gleason score and clinical setting of pretreatment evaluation was predictive of a positive RIS scan.

These analyses would suggest that RIS provides additional and independent information that correlates with the extent of disease; however, the conclusions from these studies do not directly translate into how RIS results would be used to guide management that improves 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 to support the clinical effectiveness of using RIS to evaluate pelvic lymph nodes.

Section Summary: Staging Before Curative Treatment
For pretreatment staging before curative treatment, RIS has a modest sensitivity (estimated at 50% to 75%) and a moderate to high specificity (estimated at 72% to 93%). No studies have demonstrated that use of RIS for pretreatment staging changes patient management or improves health outcomes.

Biochemical Failure after Prostatectomy or Radiotherapy
Patients who experience a rising PSA following curative treatment for prostate cancer are considered to have a recurrence; however, the location of the recurrence is sometimes not evident for a period after a biochemical failure. Localized recurrence is typically treated with salvage radiotherapy, whereas distant recurrence (i.e., metastatic disease) is usually treated with androgen deprivation therapy.

There are limited data showing that the use of RIS to evaluate patients with recurrent or residual disease can detect additional sites of disease, resulting in management decisions different from usual care. Imaging evaluation may be useful in suspected recurrence due to rising PSA levels to localize recurrent tumor and to determine whether the recurrent tumor is local to the prostate area, involves distant sites, or both. When the residual or recurrent disease is only local, patients may undergo postoperative radiotherapy, while 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 more sensitive than RIS for detecting bone metastases. 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.

Available studies are generally retrospective, descriptive reports of patterns of RIS uptake in patients with suspected recurrence. These studies, however, do not provide consistent verification of disease status, and thus the false-positive and false-negative rates in RIS studies were not well-established. While some studies have reported the percentage of cases that had associated changes in management, it is frequently difficult to determine specifically how RIS results affected management and to determine whether these changes resulted in improved net health outcomes.

A retrospective study by Raj et al (2002) included 252 patients with biochemical failure following radical prostatectomy (PSA level, ≤0.4 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% of subjects, 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 half of the patients (132/255). The study reported sensitivity and specificity rates in a small subset of
subjects (i.e., 95/252 [38%] subjects) who had some degree of verification of disease status. Reported sensitivity was 73%, and specificity was 53%. However, due to the select nature of the small subset analysis, these estimates were subject to potential verification bias and may not be considered valid measures of expected performance.

Sodee et al (2000) retrospectively analyzed 2290 RIS scans in 2154 patients with prostate cancer, either before or after treatment.11 This large multicenter study reported the rates of positive RIS scans in local, regional, and distant sites but did not provide detailed verification of results and, thus, sensitivity and specificity rates could not be determined. When the analysis was stratified by primary treatment (i.e., surgery, radiotherapy, 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 had CT scans (n=146). When CT was compared with RIS, CT did not detect pelvic or extrapelvic nodes detected by RIS in 73% of CT cases. By contrast, in a separate study (1999) of 45 subjects, RIS did not perform as well as CT in detecting metastatic disease.18

Kahn et al (1998) reported on results in 32 patients who received salvage pelvic radiation for suspected recurrence and had received RIS imaging.14 The authors reported that RIS had 50% sensitivity, 89% specificity, 78% positive predictive value, and 70% negative predictive value for detecting patients who would have tumor recurrence after irradiation. Thomas et al (2003) reported on the results of RIS in a case series of 30 men with recurrent prostate cancer treated with RT.22 They found no correlation between RIS results and tumor control, as assessed by serial PSA levels.

Liauw et al (2008) reported on 82 patients with adenocarcinoma of the prostate treated with salvage radiotherapy for an elevated PSA level after prostatectomy.23 The median PSA level before radiotherapy was 0.63 ng/mL. Of the 82 patients, 47 (57%) had a RIS (ProstaScint) scan before radiotherapy, which was used for both patient selection and target delineation. Patients with a RIS scan before radiotherapy had a lower preoperative PSA level (p=0.024) and shorter follow-up (p=0.022) than those without RIS. With a median follow-up of 44 months, the biochemical control rate was 56% at 3 years and 48% at 5 years. Margin status was the only factor associated with a biochemical control on univariate (p=0.005) and multivariate (p=0.004) analyses. Patients who had prostate bed-only uptake on RIS (n=38) did not have improved outcomes, with biochemical control rates of 51% at 3 years and 40% at 5 years. These data would support the conclusion that patients selected for treatment with RIS would not have better biochemical outcomes.

Nagda et al (2007) reported on a series of 58 patients who had ProstaScint scans as part of an assessment of rising PSA levels after prostatectomy who were then treated with prostate bed radiotherapy.24 The 4-year biochemical relapse-free survival (BRFS) rates for patients with negative ProstaScint scans (53%), positive in the prostate bed alone (45%), or positive scan findings elsewhere (74%) did not differ significantly (p=0.51). The capromab pendetide scan status did not affect BRFS. Those with a PSA level before radiotherapy of less than 1 ng/mL had improved BRFS (p=0.003). The authors concluded that the capromab pendetide scan had a low positive predictive value in patients with positive uptake elsewhere and the 4-year BRFS was similar to that for those who did not exhibit positive uptake elsewhere.

Proano et al (2006) reported on “early experience” outcomes among 44 patients with biochemical recurrence after radical prostatectomy who underwent a ProstaScint scan immediately before salvage radiotherapy.25 They noted improved prognosis (mean follow-up, 22 months) in patients who had a negative scan before radiotherapy but also noted that this finding was not necessarily independent of PSA level before radiotherapy.

Two other publications have raised questions about the accuracy (including sensitivity and specificity) of RIS, coregistered with CT, in imaging localized prostate cancer within the prostate.
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gland and in detecting seminal vesicle invasion.26,27 In a 2014 prospective evaluation of 93 patients with recurrent prostate cancer, Schuster et al reported positron emission tomography–CT with the radiotracer anti-1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid was significantly better in detecting prostatic and extraprostatic prostate cancer recurrence than RIS single-photon emission computed tomography plus CT imaging.28

Section Summary: Biochemical Failure after Prostatectomy or Radiotherapy
Numerous small case series have evaluated RIS in patients with biochemical failure after curative treatment and described rates of positivity for the local and distant disease. Limitations included the generally retrospective and descriptive nature of the studies and the lack of consistent verification of disease status. Thus, the studies do not permit accurate estimation of the false-positive and false-negative rate RIS. Moreover, no studies identified demonstrated an association between RIS findings and change in patient management or improved health outcomes in this population of patients.

Summary of Evidence
For individuals who have prostate cancer and are undergoing staging before curative treatment who receive RIS with indium 111 capromab pendetide, the evidence includes diagnostic accuracy studies and a systematic review (TEC Assessment). Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. For pretreatment staging before curative treatment, the TEC Assessment found that RIS has a modest sensitivity, estimated at 50% to 75%, and a moderate to high specificity, estimated at 72% to 93%. No studies have demonstrated that the use of RIS for pretreatment staging changes patient management or improves health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have prostate cancer and have biochemical failure after curative treatment who receive RIS with indium 111 capromab pendetide, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. The available case series were generally retrospective, descriptive, and did not provide consistent verification of disease status. Thus, the studies do not permit accurate estimation of the false-positive and false-negative rates with RIS. There is a lack of published evidence demonstrating an association between RIS findings and change in patient management or health outcomes in this population of patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines for prostate cancer (v.2.2017) do not mention ProstaScint or radioimmunoscintigraphy.29

American College of Radiology
The American College of Radiology’s 2011 Appropriateness Criteria rated the appropriateness of various imaging tests in men with rising prostate-specific antigen levels after prostatectomy or radiotherapy. Indium 111 capromab pendetide scans received a rating of 3 (defined as “usually not appropriate”).

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in August 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

References

2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Radioimmunoscintigraphy for Prostate Cancer – Update. TEC Assessments. 1998;13;Tab 21. PMID
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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes
- Laboratory reports
Post Service
- Procedure report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product 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.

IE
The following services may be considered investigational.

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<td>Planar Nuclear Medicine Imaging of Other Anatomical Region</td>
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Policy History

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

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<td>Adopted policy from BCBSA TEC</td>
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<td>Policy revision without position change</td>
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### Effective Date | Action | Reason
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11/01/2016 | Policy title change from Radioimmunoscintigraphy Imaging (Monoclonal Antibody Imaging) With Indium-111 Capromab Pendetide (ProstaScint®) for Prostate Cancer | Medical Policy Committee

### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

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 be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.