Radioimmunoscintigraphy (Monoclonal Antibody Imaging) with Indium-111 Capromab Pendetide for Prostate Cancer

Policy Number: 6.01.37  Last Review: 3/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for radioimmunoscintigraphy imaging with Indium-111 Capromab Pendetide (Prostascint®) for Prostate Cancer. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Radioimmunoscintigraphy using indium-111 capromab pendetide (Prostascint®) is considered investigational.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Individuals:**
  - With prostate cancer and undergoing staging before curative treatment
  - With prostate cancer with biochemical failure after curative treatment
| Interventions of interest are:
  - Radioimmunoscintigraphy with Indium 111 capromab pendetide
| Comparators of interest are:
  - Bone scan
  - Ultrasonography
  - Computed tomography
  - Magnetic resonance imaging
| Relevant outcomes include:
  - Overall survival
  - Disease-specific survival
  - Test accuracy
  - Test validity

Policy 6.01.37

An Independent Licensee of the Blue Cross and Blue Shield Association
Radioimmunoscintigraphy (RIS) involves the administration of radiolabeled monoclonal antibodies (MAbs), 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 prostate specific antigen (PSA).

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, a 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 rate of false-positive and false-negative 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.

**Background**

Radioimmunoscintigraphy is an imaging modality that uses radiolabeled monoclonal antibodies to target specific tissue types. MAbs 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 (SPECT).

Indium-111 capromab pendetide (ProstaScint®) (also referred to as CYT-356) targets an intracellular binding site on prostate-specific membrane antigen (PSMA) and has been approved by the U.S. 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.” Other monoclonal antibodies, directed at extracellular PSMA binding sites, are also under development.
Rationale
This evidence review on the use of radioimmunoscintigraphy (RIS) in patients with prostate cancer was created in December 2002 and based on a 1998 TEC Assessment. The review has been updated regularly with searches of the MEDLINE database, most recently through July 21, 2016.

RIS may be considered for use in a number of clinical indications. For this evidence review, 2 clinical situations will be considered:

- As part of the pretreatment workup for 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, ie, 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 (RT), 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%. Pooled data from the studies reviewed in the TEC Assessment produced an estimated 61% positive predictive value (PPV). If positive RIS results were used to exclude a patient from receiving potentially curative therapy (ie, radical prostatectomy), then 38% of patients might be harmed by inappropriately withholding the potentially curative treatment. A pooled negative predictive value (NPV) of 73% suggests that if RIS played a key role in determining that pelvic lymph nodes were clear of tumor before radical prostatectomy, then 26.7% of patients with a negative RIS scan and truly positive lymph nodes might receive potentially ineffective surgery. In addition, there is debate over a potential survival benefit with prostatectomy in the setting of positive lymph nodes. Nevertheless, in terms of evaluating the pelvic nodes, the PPVs and NPVs 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. Some of these reports appear in multiple publications, and it is possible that populations overlapped with results from multicenter studies. Moreover, the diagnostic accuracy of RIS for evaluating pelvic lymph nodes did not improve substantially over time.

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). 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 1 institution over a 4-month period. 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 curve by receiver operating characteristic analysis was 78.7%. Increasing Gleason score and clinical setting of pretreatment evaluation was predictive of a positive RIS scan.

These analyses suggest that RIS provides additional and independent information that correlates with extent of disease; however, the conclusions from these studies do not directly translate into how RIS results would actually 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 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 RT**
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 of time after biochemical failure. Localized recurrence is typically treated with salvage RT, 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 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 RT, 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 to be 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 rate of false-positive and false-negative RIS studies is not well-established. While some studies have reported the percentage of cases that 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 improved net health outcomes.

A retrospective study by Raj et al included 252 patients with biochemical failure following radical prostatectomy (PSA level, \( \leq 0.4 \) ng/mL) who had RIS performed to localize recurrence.\(^{16}\) 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 half of the patients (132/255). The study reports sensitivity and specificity in a small subset of subjects (ie, 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 selected 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 retrospectively analyzed 2290 RIS scans in 2154 patients with prostate cancer, either before or after treatment.\(^{10}\) 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 could not be determined. When analysis was stratified by whether primary treatment had been surgery, RT, 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 scanning (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 of 45 subjects, RIS did not perform as well as CT in detecting metastatic disease.\(^{17}\)

Kahn et al reported results in 32 patients who received salvage pelvic radiation for suspected recurrence and had received RIS imaging.\(^{13}\) The authors reported that RIS had 50% sensitivity, 89% specificity, 78% PPV, and 70% NPV for detecting patients who would have tumor recurrence after irradiation. Thomas et al reported on the results of RIS in a case series of 30 men with recurrent prostate cancer treated with RT.\(^{21}\) This study found no correlation between RIS results and tumor control, as assessed by serial PSA levels.
Liauw et al reported on 82 patients with adenocarcinoma of the prostate 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=0.024) 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 biochemical control on univariate (p=0.005) and multivariate (p=0.004) analysis. 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 support the conclusion that patients who were selected for treatment with RIS did not have better biochemical outcomes.

Nagda et al reported on a series of 58 patients who had ProstaScint scans as part of an assessment of rising PSA level after prostatectomy who were then treated with prostate-bed RT. 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 had no effect on BRFS. Those with a pre-RT PSA level of less than 1 ng/mL had improved BRFS (p=.003). The authors concluded that the capromab pendetide scan had a low PPV 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 reported “early experience” on outcomes among 44 patients with biochemical recurrence after radical prostatectomy who underwent a ProstaScint scan immediately before salvage RT. They noted improved prognosis (mean follow-up, 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.

Two more recent publications have raised questions about the accuracy (including sensitivity and specificity) of RIS, coregistered with CT, in imaging localized prostate cancer within the prostate gland and in detecting seminal vesicle invasion. In a 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–CT imaging.

**Section Summary: Biochemical Failure After Prostatectomy or RT**

Numerous small case series have evaluated RIS in patients with biochemical failure after curative treatment and described rates of positivity for 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 rate of false-positive and false-negative 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.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in August 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

**Summary of Evidence**
For individuals who have prostate cancer and are undergoing staging before curative treatment who receive radioimmunoscintigraphy (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, a 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 rate of false-positive and false-negative 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.3.2016) do not mention ProstaScint or radioimmunoscintigraphy.²⁸

**American College of Radiology**
The American College of Radiology (ACR) 2011 Appropriateness Criteria rated the appropriateness of various imaging tests in men with rising prostate-specific antigen levels after prostatectomy or radiotherapy.²⁹ Indium 111 capromab pendetide scans received a rating of 3 (defined as “usually not appropriate”). Among other tests included in the guideline, technetium 99m whole body bone scans were rated 8 and computed tomography (abdomen and pelvis with contrast) and magnetic resonance imaging (pelvis without and with contrast) were each rated 7. (Ratings of 7-9 are defined as “usually appropriate”).
**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**

17. Seltzer MA, Barbaric Z, Beldegrun A, et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node...


**Billing Coding/Physician Documentation Information**

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<th>Code</th>
<th>Description</th>
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millicuries

**ICD10 Codes**
Investigational for all relevant diagnoses

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<th>Description</th>
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None of these codes are exclusive to monoclonal antibody imaging.

**Additional Policy Key Words**
N/A

**Policy Implementation/Update Information**

3/1/04  Added to Policy Monoclonal Antibody Imaging:
- Radioimmunoscintigraphy using indium-111 satumomab pendetide or technetium-99m arcitumomab is considered *investigational* for but not limited to ovarian cancer, breast cancer, medullary thyroid cancer and lung cancer.
- Radioimmunoscintigraphy for prostate cancer using indium-111 capromab pendetide (*Prostascint®*) is considered *investigational*.

3/1/05  No policy statement changes.

3/1/06  Policy split into 3 separate policies:
1. Radioimmunoscintigraphy Imaging (Monoclonal Antibody Imaging) with Indium-111 Capromab Pendetide (*Prostascint®*) for Prostate Cancer
2. Radioimmunoscintigraphy Imaging (Monoclonal Antibody Imaging) Using Technetium-99m Nofetumomab Merpentan (*Verluma*)
3. Radioimmunoscintigraphy Imaging (Monoclonal Antibody Imaging) Using In-111 Satumomab Pendetide (*OncoScint*) or Tc-99m Arcitumomab (*IMMU-4, CEA-Scan*)

3/1/07  No policy statement changes.

3/1/08  No policy statement changes.

3/1/09  No policy statement changes.

3/1/10  No policy statement changes.

3/1/11  No policy statement changes.

3/1/12  No policy statement changes.

3/1/13  No policy statement changes.

3/1/14  No policy statement changes.

3/1/15  No policy statement changes.

3/1/16  No policy statement changes.

3/1/17  “Imaging and “ProstaScint®” removed from the policy title, and title changed to “Radioimmunoscintigraphy (Monoclonal Antibody Imaging) With Indium 111 Capromab Pendetide for Prostate Cancer”. No policy statement changes.
determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.