



Louisiana

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

Policy # 00419

Original Effective Date: 06/18/2014

Current Effective Date: 11/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers radioimmunoscintigraphy (RIS) using indium-111 capromab pendetide (ProstaScint[®])[†] for the evaluation and management of individuals with prostate cancer to be **investigational**.*

Background/Overview

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 1996, indium 111 capromab pendetide (ProstaScint) (also referred to as CYT-356), which targets an intracellular binding site on prostate-specific membrane antigen, 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." Other monoclonal antibodies, directed at extracellular prostate-specific membrane antigen binding sites, are also under development.

Centers for Medicare and Medicaid Services (CMS)

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.

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Rationale/Source

This review was informed by a TEC Assessment (1998).

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

STAGING BEFORE CURATIVE TREATMENT

Clinical Context and Test Purpose

The purpose of radioimmunoscinigraphy (RIS) in men with prostate cancer who are undergoing staging before curative treatment is to detect distant metastases not evident on other imaging studies because detection of occult metastases in pelvic lymph nodes is likely to alter treatment recommendations.

The question addressed in this evidence review is: Does the use of RIS improve the net health outcome in men with prostate cancer undergoing pretreatment workup for cancer staging?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is men with prostate cancer undergoing pretreatment cancer staging for curative treatment.

Interventions

The test being considered is RIS.

Comparators

The following tests are currently being used to make decisions about pretreatment workup of men with prostate cancer undergoing staging: bone scan, ultrasonography, computed tomography (CT), and magnetic resonance imaging.

Outcomes

The general outcomes of interest are overall survival, test accuracy, and tumor recurrence.

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Timing

Follow-up for post-RIS injection imaging is up to 1 week.

Setting

RIS is injected in a clinical facility certified to use radiopharmaceuticals, with imaging taking place in an outpatient setting 2 to 7 days later.

Study Selection Criteria

For the evaluation of clinical validity of the RIS, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Based on the TEC Assessment (1998) 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. 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 of 73% has 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. 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.

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Nonrandomized Studies

Since that TEC Assessment, reports have addressed the role of RIS in evaluating pelvic lymph node staging. Some of them appear in multiple publications, and population studies may overlap 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 (eg, prostate-specific antigen [PSA] level, Gleason score, clinical stage of disease). Some of these are mentioned but are not the focus of this review.

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

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence was identified addressing the clinical utility of RIS for this indication.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Analyses discussed in the section on clinical validity 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.

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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 the use of RIS for pretreatment staging changes patient management or improves health outcomes.

BIOCHEMICAL FAILURE AFTER PROSTATECTOMY OR RADIOTHERAPY

Clinical Context and Test Purpose

The purpose of RIS in men with prostate cancer and biochemical failure (ie, a rising PSA) after curative treatment is to differentiate between local and distant recurrence because local recurrence may be treated with salvage radiotherapy, while distant recurrence is usually treated with androgen deprivation therapy.

The question addressed in this evidence review is: Does the use of RIS improve the net health outcome in men with prostate cancer who experience biochemical failure after curative treatment?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is men with prostate cancer and biochemical after curative treatment.

Interventions

The test being considered is RIS.

Comparators

The following tests are currently being used to make decisions about monitoring men with prostate cancer and biochemical failure after curative treatment: bone scan, ultrasonography, CT, and magnetic resonance imaging.

Outcomes

The general outcomes of interest are overall survival, test accuracy, biochemical-free recurrence, and tumor recurrence.

Timing

Follow-up for post-RIS injection imaging is up to 1 week.

Setting

RIS is injected in a clinical facility certified to use radiopharmaceuticals, with imaging taking place in an outpatient setting 2 to 7 days later.

Study Selection Criteria

For the evaluation of clinical validity of the RIS, see the criteria outlined for the previous indication.

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Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

There are limited data showing that the use of RIS to evaluate patients with recurrent or residual disease can detect additional sites of disease better than 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. A 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.

Liau et al (2008) reported on 82 patients with adenocarcinoma of the prostate treated with salvage radiotherapy for an elevated PSA level after prostatectomy. 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.

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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. 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 pentetide 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 pentetide 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. 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 gland and in detecting seminal vesicle invasion. In a prospective evaluation of 93 patients with recurrent prostate cancer, Schuster et al (2014) 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 CT plus CT imaging.

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%, 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%. Only a minority of patients ($<20\%$) had also received a 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 (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 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. 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 (ie, 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

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patients 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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized trials were identified, and the retrospective study by Raj et al (2002), discussed above, did not report the proportion of subjects in whom patient management was altered by RIS findings.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of RIS for this indication has not been established, a chain of evidence supporting clinical utility cannot be constructed.

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 pentetide, 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.

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For individuals who have prostate cancer and have biochemical failure after curative treatment who receive RIS with indium 111 capromab pentetide, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. The available case series are generally retrospective, descriptive, and do 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.

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Policy History

Original Effective Date: 06/18/2014
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06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. New policy.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2019

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Radioimmunoscinigraphy Imaging (Monoclonal Antibody Imaging) With Indium-111 Capromab Pentetide for Prostate Cancer

Policy # 00419
Original Effective Date: 06/18/2014
Current Effective Date: 11/21/2018

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	78800, 78801, 78802, 78803, 78804
HCPCS	A9507
ICD-10 Diagnosis	C61, Z85.46

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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