Clinical Policy Title: Gallium Ga68 dotatate

Clinical Policy Number: 09.01.14

Effective Date: March 1, 2017
Initial Review Date: February 15, 2017
Most Recent Review Date: February 15, 2017
Next Review Date: February 2018

Related policies:
CP# 18.01.03 Single photon emission computed tomography (SPECT) scans

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of gallium Ga68 dotatate (Netspot®) scans to be clinically proven and, therefore, medically necessary when the following criteria are met:

- Diagnosis, staging, restaging and monitoring is necessary to guide management of neuroendocrine tumors (NETs)

Limitations:

All other uses of gallium Ga68 dotatate scans are not medically necessary and are considered investigational, including the following:

- Diagnosis, staging, restaging and monitoring of multiple myeloma (MM)

Alternative covered services:

Standard imaging modalities (e.g., computerized tomography [CT], magnetic resonance imaging [MRI], or ultrasound [US])

Background
Gallium Ga 68 dotatate is an injectable radiopharmaceutical applicable to positron emission tomography (PET) imaging, that is suitable for isolation of somatostatin receptor positive NETs. NETs are rare, sometimes malignant, tumors that develop in the hormone-producing cells of the stomach, intestines, pancreas (i.e., insulinoma) and lungs.

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on November 30, 2016. Search terms were: “gallium Ga68 dotatate.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

There is low- to moderate-quality medical evidence of safety and efficacy supportive of gallium Ga 68 dotatate PET scanning from several medium- to large-sized randomized controlled trials (RCTs)(Deppen 2016, Nockel 2016, Santhanam 2015). These trials have favorably compared imaging of NETs with the Ga 68 radiopharmaceutical to images obtained with other approved diagnostic radiography agents, and then confirmed with CT and/or MRI. Others (Alonso 2014, Tan 2014, Haug 2012, Catena 2011) evaluated Ga 68 dotatate images using histopathology and clinical follow up as reference standards; and one RCT evaluated patients with NET recurrence using Ga 68 dotatate images (Schreiter 2014). One small observational study (n=21) (Sonmezoglu 2016) opined that Gallium-68-labelled dotatate scanning may play a complementary role in MM diagnosis and management.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Deppen (2016)</td>
<td>Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors.</td>
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<tr>
<td><strong>Key points:</strong></td>
<td>An RTC inclusive of 97 adult patients (mean age 54; 41 men and 56 women) with known or suspected NETs were evaluated with Ga 68 dotatate PET.</td>
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<td>Among 78 patients in whom CT and/or MRI images and In 111 pentetreotide images were available, Ga 68 dotatate PET was in agreement with the CT and/or MRI images in 74 patients.</td>
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<td>Out of 50 patients with NETs localized by CT and/or MRI imaging, Ga 68 dotatate was positive in 48 patients including 13 patients in whom In 111 pentetreotide was negative.</td>
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<td>Ga 68 dotatate was negative in 26 out of 28 patients in whom CT and/or MRI imaging</td>
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<td><strong>Sadowski (2016)</strong></td>
<td>Prospective study of 68Ga-dotatate positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites.</td>
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</table>
| **Key points:**          | An RCT inclusive of 131 patients evaluated 68Ga dotatate PET/CT in detecting unknown primary and metastatic NETs.  
                         | 68Ga dotatate PET/CT imaging detected 95.1% of lesions (95% CI, 92.4% to 96.8%) with an average maximum standardized uptake value of 65.4 (range, 6.9 to 244), while anatomic imaging detected 45.3% of lesions (95% CI, 37.9% to 52.9%).  
                         | Over 30% of lesions (95% CI, 25.0% to 37.5%), were noted to have a significant difference between imaging modalities (P, .001).  
                         | In four of 14 patients (28.6%), 68Ga dotatate PET/CT found a previously unknown primary tumor, and detected primary NET, lymph node, and distant metastases correctly in 72 of 113 lesions (63.7%) when compared with histopathology.  
                         | On the basis of findings with 68Ga dotatate PET/CT, 43 of 131 patients (32.8%) had a change in management recommendation.  
                         | In patients with carcinoid symptoms but negative biochemical testing, 68Ga dotatate PET/CT detected lesions in 65.2% of patients.  
                         | The authors concluded that 68Ga dotatate PET/CT imaging provides important information for accurate staging of NETs and selection of appropriate treatment. |
| **Nockel (2016)**        | Localization of Insulinoma Using 68Ga-DOTATATE PET/CT Scan. |
| **Key points:**          | A retrospective analysis looked at 31 patients who were diagnosed using 68Ga-dotatate PET/CT scan and had an insulinoma confirmed on histology.  
                         | The insulinomas were correctly localized in 17 out of 31 (55%) of patients by CT, in 17 out of 28 (61%) by MRI, in 6 out of 28 (21%) by US, and in 9 out of 10 (90%) by 68Ga dotate.  
                         | In 19 out of 23 patients (83%), manual palpation identified insulinoma. In patients who had all four noninvasive imaging studies, CT was concordant with 68Ga dotatate in 6 out of 9 patients (67%); MRI in 8 out of 9 (78%); ultrasound in 0 out of 9; and in 1 out of 9 patients (11%) the lesion was only seen by 68Ga dotate.  
                         | The authors concluded that gallium 68Ga dotatate PET/CT identifies most insulinomas and may be considered as an adjunct imaging study when all imaging studies are negative and when a minimally invasive surgical approach is planned. |
| **Sonmezoglu (2016)**    | The role of 68Ga-DOTATATE PET/CT scanning in the evaluation of patients with multiple myeloma: preliminary results. |
| **Key points:**          | An observational study (n=21) looked at the role of gallium-68-labelled dotatate PET/CT scanning in patients with MM.  
                         | All patients had one or more PET-positive lesions.  
                         | There was a discordant result in four (19%) patients between scans.  
                         | Gallium-68-labelled dotatate scans showed 108 lesions in 19 patients.  
                         | No significant difference was found in terms of lesion numbers detected (P=0.67).  
                         | However, the presence of diffuse bone marrow uptake of gallium-68-labelled dotatate seems to be a predicting factor for the overall survival (P=0.033, hazard ratio: 15.2 and 95% confidence interval: 1.2-185.5).  
                         | The authors concluded that gallium-68-labelled dotatate scanning seems to be an alternative imaging modality and may play a complementary role in MM management, at least by providing a different pathobiological insight into the disease. |
| **Nakamoto (2015)**      | Additional information gained by positron emission |
| **Key points:**          | Retrospective study of 46 patients  
                         | Fourteen patients underwent a PET/CT scan for detecting unknown primary
Citation | Content, Methods, Recommendations
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Santhanam (2015) Nuclear imaging of neuroendocrine tumors with unknown primary: why, when and how? | Key points:
- Narrative review considered that NETs with unknown primary are associated with a poor prognosis (10-year survival 22%).
- There is evidence that an effort should be made to localize the primary tumor even in the presence of metastasis because resection of the primary tumor(s) may improve disease-free and overall survival.
- Localization of the tumors remains challenging and often relies on a combination of radiological, endoscopic and functional imaging.
- Newer PET radiotracers such as gallium-68-labeled somatostatin analogs such as gallium-68 dotatate have shown promise.
- In the near future, it is expected that patients with NET will benefit from newly developed PET approaches (radiopharmaceuticals) and intraoperative PET imaging.

Haug (2014) Neuroendocrine tumor recurrence: diagnosis with 68Ga-DOTATATE PET/CT | Key points:
- An RCT inclusive of 63 patients (mean age 58; 34 men and 29 women) evaluated for NET recurrence.
- Ga 68 dotatate images were interpreted independently by two central readers blinded to clinical information.
- Reader 1 correctly localized NETs in 23 out of 29 reference standard-positive patients and reader 2 correctly localized NETs in 22 such patients.
- In 34 patients with no NET identified by a reference standard, reader 1 was correct in 29 patients and reader 2 in 32.

Schreiter (2014) Searching for primaries in patients with neuroendocrine tumors (NET) of unknown primary and clinically suspected NET: Evaluation of Ga-68 DOTATOC PET/CT and In-111 DTPA octreotide SPECT/CT. | Key points:
- An RCT (n=123) evaluated the clinical efficacy of In-111 octreotide CT and Ga-68 gallium-68 PET/CT for detection of primary tumors in patients with either neuroendocrine tumor of unknown primary or clinically suspected primary NET.
- The standard of reference included histopathology or clinical verification based on follow-up examinations.
- Ga-68 gallium-68 detected primaries in 15 patients (45.5%) and In-111 octreotide in 4 patients (8%) (p <0.001); in the suspected primary NET group, only 2 primaries could be detected, all by Ga-68 dotatate.
- Primary tumors could be found significantly more often than in patients with suspected NET (p = 0.01).
- Out of these 21 patients 14 patients were operated.
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<td><strong>Tan (2014)</strong></td>
<td><strong>Diagnostic Value of 68Ga-DOTATATE PET/CT in Liver Metastases of Neuroendocrine Tumours of Unknown Origin.</strong>  The authors concluded that Ga-68 dotatate PET/CT is preferable to In-111 octreotide when searching for primary NETs.  <strong>Key points:</strong>  - An RCT of six patients (male:female = 5:1, age range 28-56 years) evaluated the diagnostic value of 68Ga dotatate PET/CT as part of a multimodality approach in neuroendocrine liver metastases of unknown primary.  - Clinical findings, histopathology, comparative imaging and follow-up were used to validate the results when ethically justified.  - Gallium 68Ga dotatate PET/CT identified the primary tumor in five out of six (83.3 %) patients: pancreas (n = 4) and stomach (n = 1).  - Out of three patients with indeterminate primary on initial CT, two patients were confirmed by 68Ga dotatate PET/CT.  - Absence of uptake in indeterminate primary of one patient was later confirmed negative by histopathology.  - In another three patients with undetected primary on initial CT, primary site was demonstrated in all patients with unsuspected metastases in two patients on 68Ga-dotatate PET/CT.  - No further work-up was done to confirm the primary in patients with distant metastases.  - Change of management was observed in three out of six (50 %) patients.</td>
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<td><strong>Alonso (2014)</strong></td>
<td><strong>Gallium (68)Ga-DOTATATE PET/CT in the evaluation of patients with neuroendocrine metastatic carcinoma of unknown origin.</strong>  <strong>Key points:</strong>  - Retrospective study of twenty-nine patients (mean age 59.5 +/- 10.6 years; female 17) with pathologically proven neuroendocrine metastases.  - In all cases conventional imaging was negative for primary tumor identification.  - Gallium (68)Ga dotatate PET/CT was performed with a mean dose of 104.2 +/- 18.8 MBq, using a 64-slice PET/CT with time-of-flight correction.  - Gallium (68)Ga dotatate PET/CT identified the primary tumor in 17/29 (59%) patients in the following locations: pancreas (n = 7), ileum (n = 7), duodenum (n = 1), colon (n = 1) and stomach (n = 1).  - Additional sites of unsuspected metastases were demonstrated in 9 patients of this group and in 6 patients in whom no primary tumor was localized, mainly in lymph nodes and mesentery.</td>
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<td><strong>Sharma (2014)</strong></td>
<td><strong>PET/CT imaging of neuroendocrine tumors with (68)Gallium-labeled somatostatin analogues: An overview and single institutional experience from India.</strong>  <strong>Key points:</strong>  - Narrative review cited NETs as rare neoplasms characterized by overexpression of somatostatin receptors (SSTRs).  - Functional imaging plays a crucial role in management of NETs.  - Authors concluded that PET-CT with gallium ((68)Ga)-labeled somatostatin analogues offers excellent results for imaging of NETs.</td>
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<td><strong>Naswa (2012)</strong></td>
<td><strong>68Ga-DOTANOC PET/CT in patients with carcinoma of unknown primary of neuroendocrine origin.</strong>  <strong>Key points:</strong>  - RCT (n=20) evaluated the role of Ga dotatate (Gallium-labeled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-Nal-octreotide) PET/CT for localization of the primary tumor in patients with carcinoma of unknown primary of neuroendocrine origin.  - PET/CT was done after injection of 132-222 (4-6 mCi) of Ga dotatate. Images were evaluated by 2 experienced nuclear medicine physicians both qualitatively as well as quantitatively (maximum standardized uptake value).  - Ga dotatate PET/CT localized the primary tumor in 12/20 (60%) patients.</td>
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### Key points:
- Even in patients in whom no primary tumor was localized, additional sites of metastatic disease were observed when compared with conventional imaging, mostly in lymph nodes and bones.
- There was a change in management in 3/20 patients (15%), who underwent surgery. In the remaining 17 patients, demonstration of somatostatin receptor expression by PET/CT made them suitable candidate for peptide receptor radionuclide therapy.

### Key points:
- An RCT (n=104) studied patients (mean age 58; 52 men and 52 women) with suspected NETs due to clinical symptoms, elevated levels of tumor markers, or indeterminate tumors suggestive of NET.
- Diagnostic performance of Ga 68 dotatate PET in localizing tumor sites was retrospectively assessed using a reference standard: histopathology (n=49) or clinical follow up of up to 5 month duration (n=55).
- Images were interpreted by consensus between two on-site readers who were not blinded to clinical information.
- NET sites were localized by reference standard in 36 patients (all by histopathology).
- Out of these, Ga 68 dotatate was positive, correctly identifying an NET site, in 29 patients and was falsely negative in seven.
- In 68 patients with no NET identified by a reference standard, the images were negative in 61 and falsely positive in seven patients.

### References

**Professional society guidelines/other:**

Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**


**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tr>
<td>D3A.8</td>
<td>Neuroendocrine tumor</td>
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<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
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<tr>
<td>A9587</td>
<td>Gallium GA-68, dotatate, diagnostic, 0.1 millicurie</td>
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