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OVERVIEW

Three radioactive tracers (florbetapir F18, flutemetamol F18, florbetaben F18) that bind to β -amyloid ($A\beta$) and can be detected in vivo with positron emission tomography (PET) have been developed. This technology is being evaluated to detect $A\beta$ neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and/or other causes of cognitive decline.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

BlueCHiP for Medicare

Coverage of amyloid PET is allowed under Coverage with Evidence Development (CED) in the Centers for Medicare and Medicaid Services (CMS) qualified clinical trial.

Original Medicare (also referred to as Medicare "fee for service") covers most of the routine costs for BlueCHiP for Medicare members participating in qualified Medicare clinical trials. All claims for services as part of a clinical trial must be submitted to Original Medicare first. Please refer to the policy for Clinical Trial Mandates in the Related Policies section below for more details.

Commercial Products

Beta amyloid imaging with positron emission tomography is not medically necessary as there is insufficient peer-reviewed scientific literature that demonstrates that the service is effective.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of coverage when services are not medically necessary or clinical research study benefits/coverage.

BACKGROUND

The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, including the presence of extracellular $A\beta$ plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnesic or nonamnesic (e.g., language, visuospatial, or executive function deficits) and a history of progressively worsening cognition over time. A diagnosis of possible AD dementia is made when the patient meets the core clinical criteria for AD dementia but has an atypical course or an etiologically mixed presentation.

Mild cognitive impairment (MCI) may be diagnosed when there is a change in cognition, but impairment is insufficient for the diagnosis of dementia. Features of MCI are evidence of impairment in 1 or more cognitive

domains and preservation of independence in functional abilities. In some patients, MCI may be a prodementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. Because clinical diagnosis can be difficult, particularly early in the course of disease, there has been considerable interest in developing biomarkers for AD. One biomarker that is being evaluated is A β plaque density in the brain detected in vivo by PET. However, A β is present in individuals without dementia, in patients with mild or subjective cognitive impairment who may or may not progress to dementia, and in patients with other types of dementia, and may be absent in a substantial proportion of patients with clinical features of AD.

PET images biochemical and physiologic functions by measuring concentrations of positron-emitting chemicals in the body region of interest. Radiopharmaceuticals used for A β imaging may be generated in a cyclotron or nuclear generator and introduced into the body by intravenous injection. A number of C and F-labeled PET radiopharmaceuticals have been investigated for imaging brain A β . However, due to their short half-life (20 minutes), C radiotracers are not convenient for commercialization. Several F A β radiotracers are currently in phase 2 and 3 clinical trials.

Regulatory Status

In 2012, the U.S. Food and Drug Administration (FDA) approved florbetapir F18 (Amyvid™; Avid Radiopharmaceuticals [a subsidiary of Eli Lilly], Philadelphia, PA) as a radioactive agent for visualizing amyloid plaque in the brain. The FDA document prepared for the advisory committee meeting indicated that although florbetapir may detect pathology, there could be no claim of disease detection, because A β aggregates can be found in cognitively normal elderly patients, as well as patients with AD.

In October 2013 and March 2014, the FDA approved 2 other radioactive diagnostic imaging agents for detecting A β plaque, flutemetamol F18 (Vizamyl™; GE Healthcare) and florbetaben F18 (Neuraceq™; Piramal Life Sciences, Matran, Switzerland), respectively.

Amyvid™, Vizamyl™, and Neuraceq™ are indicated “for PET imaging of the brain to estimate A β neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.” Prescribing information for all 3 agents states:

- The objective of A β image interpretation “is to estimate beta-amyloid neuritic plaque density in brain gray matter, not to make a clinical diagnosis.”
- A positive A β scan “does not establish the diagnosis of AD or other cognitive disorder.”
- A negative A β scan “indicates sparse to no neuritic plaques, and is inconsistent with a neuropathologic diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient’s cognitive impairment is due to AD.”
- Florbetapir, florbetaben, and flutemetamol are not intended for use in “predicting development of dementia or other neurological condition” or for “monitoring responses to therapies.”

Literature on the use of β -amyloid (A β) positron emission tomography imaging to aid in the diagnosis of patients with suspected Alzheimer’s disease is limited. A pivotal phase 3 trial, although to be commended for its use of the criterion standard of histopathology, had a number of limitations including small sample size, use of a majority rating of 3 physicians, and few patients in the mildly impaired category. This study reported a moderately high correlation of amyloid plaque with histopathologic examination. Sensitivity and specificity of this test have not yet been adequately determined in an appropriate population, including a larger number of patients with mild cognitive impairment.

Clinical utility of this technology is uncertain. The test is not likely to be useful for confirming AD in patients who present with cognitive impairment. It may have a role in ruling out AD, but this has yet to be established

with certainty. Questions also remain about the use of this test outside of investigational settings, particularly regarding the accuracy of visual interpretation of images and how best to apply this test in routine clinical practice. Therefore, this service is not medically necessary for Commercial Products.

In September 2013, CMS issued a national coverage determination that provides limited coverage for the use of A β PET imaging in 2 scenarios: (1) clinically difficult differential diagnoses, such as AD versus frontotemporal dementia, when the use of A β PET imaging may improve health outcomes and the patient is enrolled in an approved clinical study, and (2) to enrich CMS-approved clinical trials of treatments or prevention strategies for AD. CMS will cover 1 A β PET scan per patient in clinical studies that meet prespecified criteria.

CODING

BlueCHiP for Medicare and Commercial Products

The following HCPCS codes **are not medically necessary for Commercial products** and may be allowed for BlueCHiP for Medicare members as part of a CMS-approved clinical study when CMS criteria are met:

A9586

A9599

Note: If you are treating a BlueCHiP for Medicare member as part of a CMS-approved study, please follow the procedures for correct billing and coding of services found in the policy for Clinical Trials Mandate.

RELATED POLICIES

Clinical Trials Mandate

High Tech Radiology Services

Radiopharmaceuticals

PUBLISHED

Provider Update, June 2016

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