

**HEALTH EVIDENCE REVIEW COMMISSION (HERC)**  
**COVERAGE GUIDANCE: NEUROIMAGING IN DEMENTIA**

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HERC COVERAGE GUIDANCE

Screening of asymptomatic patients for dementia with neuroimaging should not be covered.

Structural neuroimaging should be covered to rule out reversible causes of dementia.\*

In patients with mild cognitive impairment, imaging should not be used to predict progression of the risk of developing dementia.

Functional neuroimaging (PET, SPECT or fMRI) should not be covered for screening, diagnosis, or monitoring of dementia.

\*Causes of potentially reversible dementia that can be detected by neuroimaging include tumors, normal pressure hydrocephalus and chronic subdural hematoma but do not include cerebral ischemia or infarcts, although these latter findings may have importance in the differential diagnosis of the subtypes of dementia.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

## EVIDENCE SOURCES

Clark, E.E., & Little, A., (2010). *Imaging in dementia*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

### *Sources Cited in MED Report:*

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National Collaborating Centre for Mental Health. (2006). *Dementia: A NICE–SCIE guideline on supporting people with dementia and their carers in health and social care*. Social Care Institute for Excellence. London: National Institute for Health and Clinical Excellence. Retrieved from <http://www.nice.org.uk/nicemedia/live/10998/30318/30318.pdf>

Scottish Intercollegiate Network of Guidelines (SIGN). (2006). *Management of patients with dementia: update*. Edinburgh: Scottish Intercollegiate Network of Guidelines. Retrieved from <http://www.sign.ac.uk/pdf/sign86.pdf>

U.S. Preventive Services Task Force. (2003). *Screening for Dementia*, Topic Page. Retrieved from <http://www.uspreventiveservicestaskforce.org/uspstf/uspstdeme.htm>

Waldemar, G., Dubois, B., Emre, M., Georges, J., McKeith, I.G., Rossor, M., et al. (2007). Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur J Neurol*, 14(1), e1-26.

Yuan, Y., Gu, Z.X., & Wei, W.S. (2009). FDG-positron emission tomography, single-photon emission tomography and structural imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: A meta-analysis. *Am J Neuroradiology*, 30, 404-410.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

## SUMMARY OF EVIDENCE

### **Clinical Background**

Dementia is a common and growing problem affecting primarily the elderly. An estimated 4.5 million people in the US had Alzheimer's disease in 2000 and the forecasted burden of Alzheimer's disease is 13 million people by 2050. Although Alzheimer's disease makes up 60-70% of dementia cases, there are other subtypes of dementia with different clinical courses and there are a small number of patients with reversible dementia.

In addition to screening laboratory tests, CT and MRI are recommended and widely used to detect intracranial abnormalities which might cause dementia. Structural (CT and MRI) and functional (PET, SPECT and fMRI) neuroimaging are currently being used to aid in the differential diagnosis of dementia subtype and to help predict those patients with milder forms of cognitive decline (mild cognitive impairment) who will progress to frank dementia.

Prior to the year 2000, most guidelines recommended MRI or CT only on a select group of patients who met clinical prediction rules. After published studies suggested that the clinical prediction rules would result in missing a few cases of reversible dementia, guidelines changed to recommend structural neuroimaging on each dementia patient at the time of initial diagnosis. Additionally, PET and SPECT began to be investigated and advocated to confirm the diagnosis of Alzheimer's dementia, distinguish between subtypes of dementia and predict the progression of dementia in patients with memory loss. The Center for Medicare and Medicaid Services (CMS) first considered coverage of PET for dementia in 2000, at which time they commissioned an AHRQ technology assessment. The conclusions of that report were that "For patients with dementia who have had a recommended clinical evaluation, treatment without further testing is superior to treatment based on an additional test using PET." In response to a request to broaden coverage of PET in dementia in 2004, CMS commissioned an update of the earlier technology assessment, which concluded that there was no additional evidence on the value of PET in differential diagnosis beyond the evidence in the 2001 technology assessment. However, an expert panel recommended limited coverage, and CMS changed its coverage policy to cover PET for patients with recently diagnosed dementia who meet the diagnostic criteria for both Alzheimer's disease and frontotemporal dementia and for whom the cause of the clinical symptoms remains in doubt in 2004.

### **Statistical Background for Interpreting the Evidence**

The statistic used to quantify the usefulness of a feature in prediction of a finding is the likelihood ratio (LR). A likelihood ratio incorporates both the sensitivity and the specificity of the test and provides a direct estimate of how much a test result will change the odds of having a disease. Sensitivity is the ability of a test to identify correctly people with a condition. A test with high sensitivity will nearly always be positive for people who have the condition. Specificity is the ability of a test to identify correctly people without a condition. A test with high specificity will rarely be wrong about who does NOT have the condition. The LR for a positive result (LR+) tells you how much the odds of the disease increase when a test is positive. The LR for a negative result (LR-) tells you how much the odds of the disease decrease when a test is negative. Likelihood positive ratios that are  $> 1.0$  increase the probability of disease and likelihood negative ratios less than 1.0 (e.g., 0.2, 0.05) decrease the probability of disease. Likelihood ratios have a large and more significant impact on the probability of disease when they are  $> 10$  or  $< 0.1$ . The odds ratio is the chance of an event occurring in one group compared to the chance of it occurring in another group. It is a measure of effect size and is commonly used to compare results in clinical trials.

## Evidence Review

### Prevalence of Reversible Dementia

There are a number of medical conditions that may present as dementia including depression, vitamin B12 (cyanocobalamin) deficiency, hypothyroidism, tertiary syphilis and some medications. These conditions can be diagnosed without the use of neuroimaging. Although causes of reversible dementia, these conditions are not considered in this report since they do not relate to neuroimaging. Causes of potentially reversible dementia that can be detected by neuroimaging include tumors, normal pressure hydrocephalus and chronic subdural hematoma but do not include cerebral ischemia or infarcts, although these latter findings may have importance in the differential diagnosis of the subtypes of dementia.

Foster (1999), a systematic review including six case series, found that potentially reversible dementia occurs in 20.7% of young (< 55 years) patients and in 5.4% of patients over 65 years. In their review, brain tumors occurred in 1% to 4% of dementia cases. Normal pressure hydrocephalus occurred in less than 2% of dementia patients and chronic subdural hematoma occurred in less than 1%. Another systematic review (Gifford 2000) also included six studies and reported prevalence rates of potentially reversible dementia that ranged from 1% to 10%.

### Role of Neuroimaging in Differential Diagnosis of Dementia

Identifying the specific sub-type of dementia may provide the treating physician and family with information about the actual diagnosis and its expected clinical course, as well as identifying whether treatment directed at preventing further cognitive decline is indicated. Although most sub-types are diagnosed based on clinical findings, there is considerable clinical overlap of symptoms and clinical course in the dementia subtypes so that proper categorization of subtype might potentially be aided by neuroimaging findings. Neuroimaging diagnosis of dementia subtypes is based on both structural and functional changes in different regions of the brain; hence both structural MRI studies and functional SPECT, PET and fMRI studies have been advocated for differential diagnosis. The sub-types of dementia include Alzheimer's disease, vascular dementia, dementia with lewy bodies and frontotemporal dementia. The sensitivity of PET for making these diagnoses is 86-96%, while the sensitivity of SPECT is 71-77% and clinical evaluation alone is 43-93%. With regard to specificity, PET is 16-87% specific, SPECT is 76-89% specific and clinical evaluation alone is 48-100% specific.

### Effect of Neuroimaging on Patient Management or Outcomes

Gifford (2000) reviewed the value of clinical prediction rules for the performance of neuroimaging in patients with dementia. Seven different clinical prediction rules were evaluated, each one including a different set of clinical findings such as presence of focal signs, headaches, rapidity of onset of symptoms, gait disorder, etc. The authors

found that the sensitivity of clinical prediction rules ranged from 25-100% and specificity ranged from 37-85%. Based on these findings the authors concluded that there is considerable uncertainty in the evidence underlying clinical prediction rules and that application of these rules may result in missed cases of potentially reversible dementia. A case series of 119 consecutive patients (Chui 1997) found that clinical prediction rules were 82% sensitive and 50% specific in predicting that neuroimaging studies would change the diagnosis. Clinical prediction rules had 5% false negatives and 36% false positives. The failure to diagnose those 5% of patients using clinical prediction rules resulted in the author's assumption that routine CT and MRI alter management by detecting cases of potentially reversible dementia. Based on the evidence addressing differential diagnosis reviewed above, any additional benefit of adding neuroimaging to clinical diagnosis on the ability to identify the correct dementia subtype appears to be small. In general, there is no evidence of improved outcomes from any neuroimaging intervention other than detecting causes of reversible dementia.

#### Role of Neuroimaging in Predicting Progression of Dementia

The prevalence data suggests that 10-15% of mild cognitive impairment patients will progress to dementia annually. Prediction of which individuals will progress using MRI, SPECT and PET is addressed by one meta-analysis (Yuan 2009) and six case series. However, without treatments that are effective at halting or reversing the progression of dementia, the ability to predict progression or prognosis may not have clinical value at this time.

Yuan (2009) evaluates PET, SPECT and MRI, and reports that pooled sensitivities for predicting progression of dementia ranged from 72-89% while specificities ranged from 70-85%. Positive likelihood ratios ranged from 2.56-4.61 and negative likelihood ratios range from 0.15-0.37. These likelihood ratios suggest small to moderate changes in probabilities. Odds ratios<sup>1</sup> ranged from 9.2-40.1. The authors concluded that PET performs slightly better than SPECT and MRI in predicting conversion of mild cognitive impairment to Alzheimer's dementia but no statistical tests were performed comparing MRI, PET and SPECT diagnostic efficacy. The individual case series had generally similar findings.

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<sup>1</sup>The odds ration in this case it represents the odds of a patient with MRI, PET or SPECT findings predictive of progression of dementia converting from mild cognitive impairment to Alzheimer's dementia compared to the odds of a patient with MRI, PET or SPECT findings predictive of non-progression. Thus a patient with a "progression" MRI has a 10.6 fold greater chance of conversion than a patient with a "non-progression" MRI (for PET the odds are 40.1 fold greater chance and for SPECT the odds are 9.3 fold greater chance of conversion).

## **Guidelines**

National Institute for Health and Clinical Excellence (NICE 2006) recommends the use of SPECT or PET when the differential diagnosis of Alzheimer's dementia, vascular dementia and frontotemporal dementia is in doubt. Scottish Intercollegiate Network of Guidelines (SIGN 2006) also recommends the use of SPECT when the differential diagnosis of dementia is in doubt.

The US Preventive Services Task Force (USPSTF 2003) recommends against screening of normal patients for dementia with any form of testing including neuroimaging.

All of the guidelines recommend the use of structural neuroimaging (CT or MRI) in the initial evaluation of patients presenting with dementia in order to rule out reversible dementia.

## **Overall Summary**

Potentially reversible dementia occurs in 20.7% of young (< 55 years) patients and in 5.4% of patients over 65 years. Clinical prediction rules aimed at identifying patients for whom neuroimaging would result in a changed diagnosis had a 5% false negative rate and 36% false positive rate. The failure to diagnose those 5% of patients using clinical prediction rules suggests that structural imaging with CT and MRI may alter management by detecting cases of potentially reversible dementia. The sensitivity of PET for diagnosing the various sub-types of dementia (86-96%) is higher than SPECT (71-77%) and potentially similar to clinical evaluation alone (43-93%). With regard to specificity, PET is 16-87% specific, SPECT is 76-89% specific and clinical evaluation alone is 48-100% specific. In general, there is no evidence of improved outcomes from any neuroimaging intervention other than detecting causes of reversible dementia. With regard to predicting progression of dementia using PET, SPECT or MRI, positive likelihood ratios ranged from 2.56-4.61 and negative likelihood ratios range from 0.15-0.37, suggesting small to moderate changes in probabilities.

## **PROCEDURE**

Positron Emission Tomography (PET) of the brain  
Magnetic Resonance Imaging (MRI) of the brain  
Functional Magnetic Resonance Imaging (fMRI) of the brain  
Single Photon Emission Computed Tomography (SPECT)

## **DIAGNOSES**

Dementia (including Alzheimer's, vascular, Lewy body and frontotemporal types)  
Mild Cognitive Impairment

## APPLICABLE CODES

<b>CODES</b>	<b>DESCRIPTION</b>
<b>ICD-9 Diagnosis Codes</b>	
191	Malignant neoplasm of brain
192.1	Malignant neoplasm of cerebral meninges
225.0	Benign neoplasm of brain
225.2	Benign neoplasm of cerebral meninges
237.5	Neoplasm of uncertain behavior of brain and spinal cord
237.6	Neoplasm of uncertain behavior of meninges
290.0	Senile dementia
290.1	Pre-senile dementia
290.4	Vascular dementia
331.0	Alzheimer's disease
331.1	Frontotemporal dementia
331.5	Idiopathic normal pressure hydrocephalus
331.82	Dementia with Lewy bodies
331.83	Mild cognitive impairment
292.82	Dementia due to drugs
432.1	Subdural hemorrhage
852.2	Subdural hemorrhage following injury without mention of open intracranial wound
<b>ICD-9 Volume 3 (Procedure Codes)</b>	
87.03	CAT scan of head
88.91	MRI of brain and brainstem
92.11	Radioisotope scan and function study: cerebral
<b>CPT Codes</b>	
70450	CT Head or brain without contrast material
70460	CT Head or brain with contrast material
70470	CT Head or brain without and with contrast material
70551	MRI Brain without contrast material
70552	MRI Brain with contrast material
70553	MRI Brain without and with contrast material
70554-70555	Functional MRI of Brain
78607	SPECT imaging of brain
78608	PET imaging of the brain
<b>HCPCS Codes</b>	
None	

Note: Inclusion on this list does not guarantee coverage

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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