

FINAL Key Questions and Background

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Background

Dementia is a broad term that describes cognitive and/or behavioral (neuropsychiatric) symptoms that affect a patient's ability to function at work or in daily activities. The patient's condition represents a decline from previous abilities and is not attributable to delirium or a major psychiatric disorder, and represents cognitive and behavioral impairment (i.e., impairment of at least two of the following: memory, reasoning/judgment, visuospatial abilities, language functions, personality/behavior). Dementia ranges in severity from mild to severe. Cognitive impairment can be detected by a combination of history-taking and cognitive assessment using mental status or neuropsychological testing. The condition of mild cognitive impairment (MCI) is primarily distinguished from that of dementia when the patient maintains the ability to function at work or in usual daily activities.

Dementia can be caused by a number of conditions and diseases. The most common cause of dementia is Alzheimer's Disease (AD), which is most prevalent in older people. Other types of dementia include vascular dementia (VaD), Lewy body dementia (which includes dementia with Lewy bodies (DLB) as well as Parkinson's Disease with dementia (PDD)), and frontotemporal dementia (FTD). Mixed dementia can also occur, in which patients have a combination of two or more types of dementia. Some forms of dementia can be reversed or treated with appropriate treatment including normal pressure hydrocephalus, subdural hematoma, tumor, thyroid problems, and vitamin B deficiency.

Diagnosis of Dementia

Patients presenting with symptoms or complaints suggestive of dementia undergo an initial evaluation consisting of a thorough history, detailed cognitive testing, and neurological examination. Most clinical practice guidelines recommend that patients who meet clinical criteria for dementia undergo at least one structural neuroimaging procedure (e.g., computed tomography (CT) or magnetic resonance imaging (MRI) scan) and laboratory testing to exclude reversible causes of dementia such as subdural hematoma or tumor. Structural neuroimaging may also aid in the diagnosis of dementia subtype based on patterns of atrophy. After this initial comprehensive work-up, a specific diagnosis is generally able to be made. However, in some patients the diagnosis remains unclear and additional testing with functional imaging may be conducted in order to make an accurate diagnosis.

Technology of Interest

Functional neuroimaging involves the injection into the blood of radiolabeled ligands. The radiolabeled ligands flow in the blood supply to the brain and are then detected by a scanner allowing visualization of the blood supply within the brain. Types of functional neuroimaging include single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI). Because cerebral blood flow correlates with brain metabolism, the images provide information regarding which regions of the brain are affected, which in turn may aid with differential diagnosis. FDG (fludeoxyglucose) PET also provides information regarding brain metabolism by measuring glucose uptake. Functional neuroimaging is an add-on diagnostic test that is typically only done in addition to

structural neuroimaging if needed to determine or confirm a diagnosis that remains uncertain following usual testing. In contrast to structural imaging, functional neuroimaging may provide specific information regarding specific brain functions.

Functional neuroimaging has the capability of aiding in the differential diagnosis of AD, DLB, and FTD disorders (including primary progressive aphasia (PPA)). Functional neuroimaging is not typically used in the diagnosis of vascular dementia due to the high resolution and ability of MRI to show subtle vascular changes in white matter, although it could be used to detect AD or FTD in a patient with dementia and vascular disease for whom the diagnosis was not clear. While functional imaging is typically not used to diagnose mild cognitive impairment, it may predict future conversion to AD and thus would help patients plan for the future. It is anticipated that if effective therapies for dementia, including AD, are discovered in the future, they would likely be most effective in the earlier stages of the disease. Should this occur, the availability of functional imaging for those with mild cognitive impairment would be very important.

Policy Context:

There are significant questions related to the use of functional neuroimaging for the diagnosis of primary neurodegenerative dementia and mild cognitive impairment, specifically, there are medium concerns regarding safety, efficacy, and cost.

Scope of This HTA:

Population

Patients with dementia or mild cognitive impairment who have undergone a comprehensive initial diagnostic work-up including structural neuroimaging. Diagnoses of interest include primary neurodegenerative dementia, including:

- Alzheimer's Disease (AD), including atypical AD
- Lewy body dementia, including dementia with Lewy bodies (DLB) and Parkinson's Disease with dementia (PDD)
- Frontotemporal dementia (FTD) disorders, including: behavioral variant FTD (bvFTD); corticobasal degeneration (CBD); FTD with motor neuron disease (FTD/MND); Pick's Disease; primary progressive aphasia (PPA); progressive supranuclear palsy (PSP)
- Mild cognitive impairment (MCI)

Index Test

Diagnostic functional neuroimaging modalities include:

- PET (positron emission tomography) to measure glucose metabolism (e.g., ^{18}F -FDG-PET)
- SPECT (single photon emission computed tomography) to measure cerebral perfusion (e.g., $^{99\text{m}}\text{TC}$ -HMPAO-SPECT) and dopamine transporter uptake (e.g., ^{123}I -FP-CIT-SPECT, ^{123}I -ioflupane-SPECT, Dat-SCAN)
- fMRI (functional MRI)

Comparator Test(s)

- Gold standard (histopathological confirmation or genetic confirmation if applicable) (KQ1)
- Direct comparison of functional neuroimaging methods with each other (e.g., FDG-PET vs HMPAO-SPECT) (KQ2)

- Comprehensive initial diagnostic work-up (to include structural neuroimaging (KQ2 (first part), KQ3, KQ5, KQ6))

Outcomes

- Primary outcomes of interest: Patient progression; patient health outcomes including function, quality of life, behavioral and psychological outcomes; harms from neuroimaging procedure; cost-effectiveness
- Intermediate or secondary outcomes: Diagnostic accuracy measures; patient health outcomes including cognition, depression, caregiver burden, and global outcome measures; impact on therapeutic decisions or clinical management

Contextual Questions:

What is the reliability and accuracy of functional neuroimaging (e.g., SPECT, PET, and fMRI) as used to diagnose AD, FTD, and Lewy body dementia (including DLB and PDD) in symptomatic dementia patients who have undergone a comprehensive initial diagnostic work-up (that included structural neuroimaging). Specifically:

- Provide a summary of the inter-rater and intra-rater diagnostic reliability (reproducibility).
- Provide a summary of the sensitivity and specificity based on an appropriate gold standard (e.g., autopsy, genetic confirmation).

Key Questions:

1. What is the diagnostic accuracy of functional neuroimaging for the differential diagnosis of AD, FTD, and Lewy body dementia (including DLB and PDD) based on an appropriate gold standard (e.g., autopsy, genetic confirmation)?
2. What is the ability of functional neuroimaging to predict progression and clinical outcomes? Is one functional test better at predicting progression or clinical outcomes versus another?
3. Do the results of functional neuroimaging impact therapeutic decisions or clinical management compared to those made for patients who did not receive functional neuroimaging?
4. What are the short and long term harms of diagnostic functional neuroimaging?
5. What is the evidence that functional neuroimaging may perform differently in subpopulations (i.e., younger age, presence of comorbidities, etc.)? Consider the impact on disease progression, clinical outcomes, and harms.
6. What is the cost-effectiveness of incorporating diagnostic functional neuroimaging into the comprehensive initial diagnostic work-up?