Technology Assessment

Technology Assessment Program

POSITRON EMISSION TOMOGRAPHY, SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY, COMPUTED TOMOGRAPHY, FUNCTIONAL MAGNETIC RESONANCE IMAGING, AND MAGNETIC RESONANCE SPECTROSCOPY AND FOR THE DIAGNOSIS AND MANAGEMENT OF ALZHEIMER'S DEMENTIA.

April 30th, 2004

Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, Maryland 20850

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POSITRON EMISSION TOMOGRAPHY, SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY, COMPUTED TOMOGRAPHY, FUNCTIONAL MAGNETIC RESONANCE IMAGING, AND MAGNETIC RESONANCE SPECTROSCOPY AND FOR THE DIAGNOSIS AND MANAGEMENT OF ALZHEIMER'S DEMENTIA.

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Summary

In December of 2001, the Duke Evidence Practice Center (EPC) completed a technology assessment to review the existing scientific evidence with regard to the role of 2-Fluoro 2-deoxy D-glucose Positron Emission Tomography (FDG-PET) in assisting with the diagnosis of early dementia in elderly patients for whom the differential diagnosis included one or more kinds of neurodegenerative disease. There were two main conclusions 1) PET improves the overall accuracy of diagnosis compared to accuracy of an examination based on American Academy of Neurology (AAN) guidelines and 2) treatment based on a standard AAN-recommended examination leads to better health outcomes than treatment based on PET results. This result was robust to a broad range of assumptions. Based on the assumption that new data may have been published since 2000 that may impact these original findings, CMS requested an update of the technology assessment.

In order to identify literature that would clarify the role of FDG-PET for use in these patients, a revised review was conducted to address three separate areas in which PET might be useful: diagnosis, prognosis and response to therapy. Twenty-two studies were initially identified for abstract review. Based on a review of these studies, including references

and input from experts, four studies were identified for full text review. One examined the use of PET in distinguishing Parkinsonian dementia from AD (Bohnen, 2003). Three other studies described the ability of FDG-PET to predict progression to AD in patients with mild cognitive impairment (Chetelat, 2003; Arnaiz 2001; Silverman 2003).

Of the four studies identified for full text review, one examined the use of PET in distinguishing Parkinsonian dementia from AD (Bohnen, 2003). The three other studies described the ability of FDG-PET to predict progression to AD in patients with mild cognitive impairment (Chetelat, 2003; Arnaiz 2001; Silverman 2003).

Based on a review of these articles, there are two conclusions. 1) Publications since the prior TA do not provide evidence supporting revised estimates of the operating characteristics of PET for discriminating AD from other competing diagnoses. 2) Three studies suggest FDG-PET could be valuable for distinguishing patients with MCI who rapidly convert to frank AD. Two were relatively small studies that require validation and assessment of incremental value above conventional clinical measures. A third, larger study of FDG PET for prediction of progression for patients with MCI also suggests a potential role for PET in predicting clinical course for patients with dementia. However, this study did not comment on findings

for patients with AD only, and results for PET, while suggestive of higher sensitivity and specificity, did not differ in a statistically significant manner from clinical findings.

In addition, CMS requested that the Duke EPC review and summarize in the form of an annotated bibliography, the existing scientific evidence with regard to the role of single-photon emission CT (SPECT), volumetric assessment by computed tomography or magnetic resonance imaging (Volumetric CT/MRI), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS) in the diagnosis, prognosis and estimates of responsiveness to treatment for patients with cognitive abnormalities. Of 472 articles initially identified for abstract review, 12 articles for SPECT, 9 for Volumetric CT/MRI, 2 for fMRI, and 4 for MRS eventually met all inclusion criteria and are summarized as an annotated bibliography.

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1. INTRODUCTION

1.1 Overview

In December of 2001, the Duke Evidence Practice Center (EPC) completed a technology assessment to review the existing scientific evidence with regard to the role of 2-Fluoro 2-deoxy D-glucose Positron Emission Tomography (FDG-PET) in assisting with the diagnosis of early dementia in elderly patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. This technology assessment informed a decision by the Centers for Medicare & Medicaid Services (CMS). CMS is now reconsidering this decision and has requested an update of the technology assessment.

In addition, CMS has requested that the Duke EPC review the existing scientific evidence with regard to the role of single-photon emission CT (SPECT), volumetric assessment by computed tomography or magnetic resonance imaging (Volumetric CT/MRI), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS) in the diagnosis, prognosis and estimates of responsiveness to treatment for patients with cognitive abnormalities.

1.2. Request by the Centers for Medicare and Medicaid Services

The Duke EPC was asked by the Agency for Health Care Research and Quality (AHRQ) to conduct an assessment to answer two questions raised by the Centers for Medicare & Medicaid Services (CMS):

1. What is the new clinical data on the use of PET in the diagnosis of early dementia in elderly patients published since 2001, the end date for the previous technology assessment (TA)? The new TA should include any articles on use of PET to distinguish patients with AD from those with other causes of symptoms confounding the diagnosis of dementia, or to assist with the diagnosis of early dementia in individuals for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. The TA will include a summary of the data, a critical appraisal of the quality of the studies, and an analysis of how these new data might change the 2001 analysis.

2. What clinical data is available on the use of SPECT, Volumetric CT/MRI, fMRI and MRS in the diagnosis of early dementia in elderly patients, published after 1995? The response to this questions should

be a structured, annotated review, organized by key issues for policy makers, including the following:

a. Studies on the use of the technology to discriminate between AD and other causes of cognitive impairment
b. Studies that predict prognosis for the natural history of disease
c. Studies that predict response to treatment, in terms of both positive and adverse effects

In addition, we sought studies on potential harms and benefits of testing and the "value of knowing" (i.e. impact of being told test results – positive or negative – on non-medical decision making and general quality of life).

1.3. Structure of the Evidence Report

In order to address the questions posed by CMS and for ease in reading and comprehension, the report is separated into two sections corresponding to the two questions. The first section is an updated literature review regarding the role of FDG-PET in the diagnosis of dementia in elderly patients and is organized as follows:

A brief overview of the goals and results of the previous TA (Matchar, 2001) is followed by a discussion of methods used to identify and review new literature. This is followed by a detailed description of articles meeting all inclusion criteria. The section is concluded by a summary statement regarding the effect the update has on the original report.

The second section addresses the second question regarding clinical research studies on the use of SPECT, Volumetric CT/MRI, fMRI and MRS in the diagnosis, prognosis, and predicted treatment response of early dementia in elderly patients. After a brief overview of the issues addressed in the literature and rationale for the overall organization of articles within the report, the technologies assessed and their application in patients with cognitive impairment is described. A methods section outlines the literature search, detailed inclusion criteria and a list of characteristics reported for each evaluated article. The results section is organized by application of the technologies (i.e., diagnosis, prognosis, or predicted response to treatment). Within each application the studies are listed by Fryback and Thornbury categories (Fryback, 1991) (described in more detail below, Section 2.2.3).

2. UPDATED REVIEW OF THE LITERATURE REGARDING FDG-PET IN DIAGNOSING DEMENTIA

2.1 Original Technology Assessment

The goal of the original TA was to assess the benefits of FDG-PET scanning in patients with dementia, with mild cognitive impairment (MCI) and in asymptomatic patients with a family history of AD, subsequent to the standard evaluation as described in the American Academy of Neurology (AAN) guidelines. The assessment was accomplished by reviewing the scientific evidence regarding the performance of PET, natural history of AD, treatment efficacy and adverse effects, and creating a decision model linking testing with treatment and outcomes. The methods and results are described in detail in an evidence report (Matchar, 2002) that is available online from: http://cms.hhs.gov/coverage/download/8b3-ww3.pdf).

The findings of the original TA are consistent with previously published evidence reviews tied to models (Silverman,2001; MacMahon, 2003); namely that PET improves the overall accuracy of diagnosis compared to accuracy of an examination based on AAN guidelines. Also consistent with MacMahon et al. (2003), but in contrast to Silverman et al. (2001), the original TA concluded that treatment based on a standard AAN-

recommended examination leads to better health outcomes than treatment based on PET results, and that this result is robust to a broad range of assumptions. The apparent discordance between overall accuracy and clinical benefit relates to two points recognized in both the original TA and in the MacMahon, et al analysis. First, the efficacy of currently available treatments, such as anticholinesterase inhibitors (AChEIs), has been established from trials using an examination based on AAN guidelines as the reference standard. Thus, treatment restricted to patients with a diagnostic PET result will necessarily decrease the number of patients with AD who are treated (i.e., PET results in more false negatives than an examination based on AAN guidelines); these patients will not benefit from delayed AD progression due to treatment. Second, while PET use will decrease the number of patients incorrectly labeled as having AD (and will decrease the number of these false positives more than it will increase the number of false negatives), this benefit of fewer false positives is relatively less important since AD treatments are generally benign. It is important to note that these points remain relevant for evaluation of patients who have not yet developed frank AD (since presumptive treatment may provide an even greater net benefit if it delays the onset of even mildly disabling

symptoms), and for patients who are evaluated by clinicians less skilled in diagnosis of cognitive symptoms.

Three additional insights emerged from the original TA regarding *when* testing would be expected to improve clinical outcomes.

First, testing would be an attractive option if a new treatment becomes available that is not only more effective than AChEIs but is also associated with a risk of severe adverse effects. However, to our knowledge, no such treatment is currently available.

Second, testing would be useful if it could be demonstrated to be a better reference standard than an examination based on AAN guidelines. To the point, testing would need to better distinguish patients who respond to therapy than is possible with a standard examination. No evidence was uncovered in the original TA to indicate this was the case.

Third, testing could be useful if the results could be shown to have benefits beyond informing AchEI use. This "value of knowing" could have

both positive and negative components. In any case, no PET research was identified that examines this issue empirically.

Based on these insights, we conclude that, in addition to estimating the operating characteristics of tests for the diagnosis of AD, it is crucial to understand the value of testing for estimating disease prognosis, and for predicting response to treatment (in terms of both positive and adverse effects). Here, value could include the value of knowing health status, exclusive of the utility of this information in choosing therapy.

2.2 Methods

2.2.1. Overview of the literature search

The original literature search, conducted using MEDLINE was updated to include articles that were published during and after 2001. In addition, we searched the International Network of Agencies for Health Technology Assessment (www.inahta.org) database, the National Institute for Clinical Excellence database (www.nice.org.uk), the Health Technology Assessment database (www.hta.nhsweb.nhs.uk), and the Guidelines International Net database (www.g-i-n.net) to identify pertinent evidence reports or technology assessments that may have been published in the

last 3 years. References from recently published literature reviews were also searched to identify any additional technology assessments or evidence reports. The results of these searches are documented below.

2.2.2. Search strategy

The following is the search strategy using Ovid MEDLINE

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1 exp *alzheimer disease/di, ra (2622)
2 exp tomography, emission-computed/ (32749)
3 and/1-2 (190)
4 fdg-pet.mp. (2163)
5 1and 4.mp. [mp=title, abstract, name of substance, mesh subject heading] (0)
6 or/3,5 (190)
7 limit 6 to yr=2001-2004 (57)
8 6 not 7 (133)
9 pet.tw. (16087)
10 fdg-pet.tw. (2163)
11 exp alzheimer disease/ (31076)
12 exp "sensitivity and specificity"/ (149939)
13 or/2,4,9-10 (38029)
14 or/1,11 (31076)
15 and/13-14 (1195)
16 12 and 15 (110)
17 6 or 16 (273)
18 limit 17 to human (269)
19 limit 18 to english language (228)
20 discriminant analysis/ (3400)
21 20 and 15 (13)
22 risk factors/ (227494)
23 22 and 15 (33)
24 case control studies/ (52837)
25 24 and 15 (61)
26 Diagnosis, differential/ (239645)
27 26 and 15 (146)

28 or/21,23,25,27 (235)
29 28 not 17 (149)
30 limit 29 to human (149)
31 limit 30 to english language (129)
32 limit 31 to yr=2001-2004 (22)
33 from 32 keep 1-22 (22)

2.2.3. Results of the literature review and inclusion criteria for full text article identification

No recently published TAs were listed in any of the four websites. However, two TAs were identified based on a recent review of the literature by Gill et al. (2003) (Veteran's Health Administration, 2001; Institute for Clinical Evaluative Sciences, 2001). A review of the publications included in these technology reports did not yield new studies for inclusion, beyond those provided in our prior evidence report (Matchar, 2001)

The MEDLINE search resulted in 22 potential articles for review. Consistent with the inclusion criteria used in the original TA (Matchar, 2001) only articles that were considered Category 2 or higher using the classification scheme developed by Fryback and Thornbury (Fryback, 1991) were included for full text review. Table 1 summarizes these categories. An exception was made in the original report for Level 1

articles that examined the use of FDG-PET in AD patients and controls; these articles were included to determine the test characteristics of FDG-PET. However, for this TA, we excluded articles describing the performance of PET in patients with AD compared to normal controls. We did this for two reasons. First, such studies do not directly address the relevant clinical issue – discriminating between etiologies of cognitive symptoms – since by design the imaging study could not provide diagnostic or prognostic information beyond that available from clinical evaluation. Second, evidence from our previous review indicates that comparisons of AD and clinically normal patients leads to biased estimates of sensitivity and specificity for discriminating between AD and other etiologies of cognitive impairment. On this basis, 4 articles were identified for full text review and are described in detail in the next section.

Table 1. Fryback et al. Classification Categories (1991)

CLINICAL QUESTION	CATEGORIES	CATEGORY DESCRIPTION	MEASURES
Does the test have good technical characteristics that make it appropriate for use in a clinical setting?	1	Technical feasibility and optimization	Ability to produce consistent spectra
Does the test have good operating characteristics that make it useful for 1) determining the presence of disease? 1) determining the severity of disease? 2) improving the yield of specimens for diagnosing disease?	2	Diagnostic accuracy	Sensitivity and specificity % yield of abnormal diagnoses
Does the test influence the clinicians' subjective assessment of disease status?	3	Diagnostic thinking impact	Difference in clinician's subjectively estimated diagnosis probabilities pre and post-test
Does the test influence the therapy given to a patient?	4	Therapeutic choice impact	% of times therapy planned prior to PET changed after PET
Does the test result in an improvement in life expectancy from the patient viewpoint?	5	Patient outcome impact	% of patients who improved with PET compared to % without PET Cost per QALY saved with image information
Does the test result in an improvement in life expectancy at a reasonable cost from the viewpoint of society?	6	Societal impact	Cost-benefit or cost-effectiveness analysis conducted from a societal viewpoint

2.3 Results

Of the four studies identified for full text review, one examined the use of PET in distinguishing Parkinsonian dementia from AD (Bohnen, 2003). The three other studies described the ability of FDG-PET to predict progression to AD in patients with mild cognitive impairment (Chetelat, 2003; Arnaiz 2001; Silverman 2003).

Bohnen et al (2003) used PET to examine cortical cholinergic function in patients with Parkinsonian Dementia (PDem) (n=14), AD (n=12), Parkinson's disease without dementia (PD) and normal controls (n=10), based on earlier pathologic findings that suggested that patients with PDem have cholinergic forebrain neuronal losses that may be equivalent or greater than losses seen in patients with AD. [11C] PMP radioligand was used in conjunction with PET to determine AChE activity in the four groups. PET was conducted using an ECAT HR+ (CTI PET Systems, Knoxville, TN). Regions of interest were determined using co-registration with MRI. AD patients were recruited from the Alzheimer's Disease Research Center at the University of Pittsburgh and diagnosed using the Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA). Patients with

PD or PDem were recruited from the Movement Disorders Clinic at the University of Pittsburgh and were diagnosed using the Consortium on Dementia with Lewy Bodies criteria. Compared with controls, mean cortical AChE activity was lowest in patients with PDem, followed by patients with PD without dementia. Mean cortical AChE activity was relatively preserved in patients with AD, except for the lateral temporal cortex, suggesting that reduced cortical AChE activity may be more characteristic of patients with PDem than those with AD.

Chetelat et al. (2003) examined 17 patients with MCI at 6-month intervals for 18 months to determine a metabolic profile that could be used to predict progression to AD. Patients were classified as MCI if they did not meet the criteria for probable AD using the NINCDS-ADRDA criteria and had Mini-Mental Status Examinations (MMSE) with scores of $\geq$24. The authors theorized that, based on prior studies, the earliest metabolically affected areas in patients with probable AD was the posterior cingulate gyrus (PCG) followed by the temporoparietal posterior association cortex and hippocampal region. For comparison, 15 healthy controls without memory impairment were included. FDG-PET scans were obtained at entry and at each followup visit (12 months and 18 months) using the

ECAT HR+ device (CTI, Knoxville, TN). Statistical parametric testing was used in determining regional activity values. These values were in turn used to determine the percent of patients correctly classified as converters and non-converters. The authors examined the results using a specified a cut-off. However, they do not make it clear if the cut-point value was determined *a priori* or was based on multiple comparisons. Neuropsychological testing was also conducted at baseline and at follow up, using scales to assess global functioning (Mattis), attention, verbal initiation, motor initiation, visuospatial construction, conceptualization, memory, total recall (Grober and Buschke) and delayed recall (Ray's figure), blinded to PET results. Of the original 17 patients, 7 eventually met the inclusion criteria for probable AD. These 7 patients were termed rapid converters. Compared to non-converters, these patients were shown to have significantly lower FDG uptake, at inclusion, in the temporoparietal posterior association cortex and based on the described cut-point differentiated all converters from all non-converters. The PCG appeared to provide only marginal differentiation. During the 18 months of followup, this area continued to be significantly associated with rapid conversion suggesting its potential usefulness in distinguishing MCI rapid converters from non-converters.

Arniaz et al. (2001) followed 20 patients with MCI to determine whether reduced glucose metabolism could be used to predict progression to AD. No controls were included in this study. FDG-PET scans were obtained at entry and at approximately 3-month intervals using two scanners, the GEMS 2048-15B and GEMS 4096-15WB (General Electric Medical Systems, Milwaukee, Wisc). Neuropsychological testing was also conducted at baseline and at follow up, using scales to assess global functioning (MMSE), intelligence (information, digit span, similarities, block design and digit symbol from the Wechsler adult intelligence scale-revised), trail making tests, the Rey-Osterreith copy and retention test, the Rey auditory verbal learning test and the free recall and recognition of words from the Stockholm Geriatric Research Center. Of the original 20 patients, 9 eventually met the inclusion criteria for probable AD using the NINCDS-ADRDA criteria. Compared to patients who did not convert, converters had significantly lower baseline results in block design, digit symbol and trail making B time. They also had significantly lower uptake values in the left temporoparietal regions above the level of the basal ganglia. Using logistic regression, the authors explored different statistical models using imaging in combination with the various neuropsychological testing results to predict

progression. Two variables that were consistently and significantly associated with progression were left temporoparietal glucose metabolism and performance on the block design test. These measures correctly classified 90% of patients as converters and non-converters, whereas use of either by itself gave 75% (glucose metabolism) and 65% (block design) correct classification, suggesting their potential combined use in determining progression in patients with MCI. No model examined the incremental contribution of PET to clinical findings.

Silverman et al. (2003) retrospectively assessed 167 patients with cognitive impairment referred to an academic nuclear medicine clinic for brain PET, to determine whether reduced glucose metabolism could be used to predict dementia progression. FDG-PET scans were obtained at baseline using two scanners, the Siemens/CTI ECAT 831 or 931 or the Siemens ECAT EXACT HR or HR+ scanner (CTI PET Systems, Knoxville, TN). Physicians who were blinded to clinical follow-up data read the scans and classified them as progressive or non-progressive based on criteria established a priori. Scans considered positive for signs of progression had focal cortical hypometabolism in parietal, temporal and frontal lobes, or diffuse cortical hypometabolism with sparing of sensorimotor ± visual

cortex, with cortical deficits unaccounted for by matched findings on CT or MRI indicative of cerebrovascular disease. Negative scans had no abnormal findings or had abnormal findings other than those meeting the definition of a positive scan. Clinical data was based on chart review and a study questionnaire. Information recorded included handedness, indication for PET, originally reported PET findings, reported findings of CT or MRI, functional, behavioral and cognitive status, elapsed time between date of PET scan and patient's most recent evaluation during which cognitive status could be assessed and any neuropathological findings. Progression was assessed using neuropsychiatric data obtained at least 2 years following the initial PET or at least 3 years later for patients taking cholinesterase inhibitors. Progression was independently confirmed by two board certified physicians blinded to PET findings. Since MMSE score was the most widely utilized measure across patients, scores were compared for progressors and non-progressors. Patients considered to be progressors using criteria for the PET scans had an average 4.1 points lower MMSE score (compared to baseline) whereas non-progressors had an average difference of 2.1 points over the same interval although these differences were not statistically significant. One hundred and twenty eight patients also had clinical data available for assessment of progression

obtained at the time of PET. Of these, 58 were classified as having progressive dementia using clinical criteria, 44 were classified as having a non-progressive dementia and 26 had an indeterminable diagnosis. Of the 102 patients with a clinical diagnosis 64 patients were eventually considered to have met the criteria for progression; 38 patients were considered non-progressors. The sensitivity of clinical exam for predicting progression 77% (95%: CI 66-87%) and specificity was 76% (95%CI: 63-90%). For this same group of patients, sensitivity of PET was 95% (95%: CI 90-100%) and specificity was 79% (95% CI: 66-92%). Information on specific cause for progression was not presented.

2.4 Conclusions

Publications since the prior TA do not provide evidence supporting revised estimates of the operating characteristics of PET for discriminating AD from other competing diagnoses. The one included study examined a variant of PET involving a radioligand other than FDG and thus is not clearly relevant to current or near-term clinical practice. Three studies suggest FDG-PET could be valuable for distinguishing patients with MCI who rapidly convert to frank AD. Two were relatively small studies that require validation and assessment of incremental value above conventional

clinical measures. A third, larger study of FDG PET for prediction of progression for patients with MCI also suggests a potential role for PET in predicting clinical course for patients with dementia. However, this study did not comment on findings for patients with AD only, and results for PET, while suggestive of higher sensitivity and specificity, did not differ in a statistically significant manner from clinical findings.

3. USE OF SPECT, VOLUMETRIC CT/MRI, fMRI AND MRS IN AD DIAGNOSIS, PROGNOSIS AND TREATMENT RESPONSE MONITORING

3.1 Overview

This section addresses the second question posed by CMS: To produce a structured annotated bibliography on the use of SPECT, Volumetric CT/MRI, fMRI and MRS (in early dementia). The annotated bibliography is organized by key issues for policy makers:

a. Studies on the use of the technology to discriminate between AD and other causes of cognitive impairment
b. Studies that predict prognosis, including studies on potential harms and benefits of testing and the "value of knowing"
c. Studies that predict response to treatment, in terms of both positive and adverse effects.

3.2 Technology Background

The technologies listed by CMS for review are SPECT, Volumetric CT/MRI, fMRI and MRS. The following describes why each of these technologies is potentially relevant to diagnosis, prognosis, and prediction of response to treatment.

Single-Photon Emission Computed Tomography (SPECT)

SPECT is used to evaluate regional brain perfusion. In this application, a ^{99m}technetium-based lipid soluble radionuclide, such as hexamethylpropylene amine oxime (HMPAO), crosses the blood brain barrier in proportion to cerebral blood flow (Neirinckx,1987). Emission data is collected using a rotating gamma camera and is processed to generate a perfusion image. These images are generally evaluated semiquantitatively by regions of interest (ROIs). Relative regional cerebral blood flow (rCBF) is calculated for each ROI based on mean counts compared to a reference area such as the cerebellum (Pickut, 1999).

Like PET, patients with AD often demonstrate reduced activity (here reflected in a reduction in the posterior parietal and temporal lobes). Similarly, different types of dementia may be associated with different patterns of rCBF; for example, individuals with vascular dementia would be expected to have patchy perfusion deficits. SPECT has a lower spacial resolution than PET. Like PET, individuals with less severe cognitive impairment are less likely to have abnormal results (Matchar, 2001).

Volumetric (Quantitative) Magnetic Resonance Imaging and Computed Tomography (Volumetric CT/MRI)

There is general brain atrophy associated with aging in the absence of cognitive impairment and measures of general brain volume have not been promising as an indicator of AD (Petrella, 2003). However, evidence indicates that atrophy of the medial temporal lobes, particularly the hippocampus and the entorhinal cortex, is particularly common for patients with AD, including those at the earliest stages (Jack, 1999). Because of the uneven shape and size of these areas, the current approach to assessing possible AD-related atrophy is to use MRI to estimate quantitative hippocampal volume derived from semiautomated computer algorithms. To further improve the technique, serial measurements can be performed with the expectation that rate of hippocampal atrophy will better identify individuals who have AD and who will progress more rapidly. One innovation in the interpretation of these serial images is the use of a nonlinear registration algorithm that, with a theoretical model of the deformation of a compressible viscous fluid, produces a color map of brain atrophy (Fox, 2001).

MRI is a widely available technology. However, volumetric assessment is not yet fully automated and is thus subject to observer variation. Further, the semiquantitative approaches are time-consuming.

CT has also been used in volumetric assessment. However, unlike MRI, CT is hampered by bone hardening artifact and limited view angle; it is used to visualize enlargement of the temporal horns and widening of the hippocampal fissures as indirect changes due to atrophy of the hippocampus.

Functional Magnetic Resonance Imaging (fMRI)

fMRI, also called blood oxygenation level-dependent MRI (BOLD MRI), is based upon the observation that neuronal activation increases blood flow, and thus oxyhemoglobin delivery, to active areas of the brain (Corkin, 1998). The increase in oxygen delivery exceeds tissue oxygen requirements of firing neurons, leading to a reduction in the venous concentration of deoxyhemoglobin (Dijkhuizen, 2003). This reduction in deoxyhemoglobin is detected by fMRI as an increase in signal intensity (Corkin, 1998; Dijkhuizen, 2003; Rosen, 2002).

The medial temporal lobe (MTL) is the site of early brain injury in patients with AD. The MTL has multiple subregions and defining these subregions requires high-resolution spatial imaging. Moreover, in order to observe responses to stimuli, functional imaging requires high temporal resolution (Corkin, 1998; Dijkhuizen, 2003; Rosen, 2002). In order to accommodate the requirement for both high spacial and high temporal resolution, fMRI is performed in two steps. The first step is a very high resolution structural scan using standard MRI techniques. Guided by any structural abnormalities identified on the structural scan, the second step, the functional scan, is performed (Corkin, 1998; Dijkhuizen, 2003; Rosen, 2002). During the functional scan the patient is presented with active or passive stimuli (Dijkhuizen, 2003; Rosen, 2002). In active stimulation the patient is engaged in cognitive tasks. In passive stimulation the patient is exposed to external stimuli but does not intentionally perform cognitive tasks. If increases in signal intensity are correlated temporally with the performance of cognitive tasks then the area is considered functionally active (Dijkhuizen, 2003; Rosen, 2002). Some studies have shown that individuals with AD have increased functional activation of certain brain areas than healthy controls, but this was also true for healthy older adults (Wagner, 2000). Another study found that a decrease in memory scores

over a two-year period correlated with the number of active regions on fMRI (Wagner, 2000).

fMRI is safe and since there is no radiation, as there is with PET, it can be performed repeatedly over short periods of time (Rosen, 2002). This permits a more accurate assessment of temporal changes (Rosen, 2002). fMRI also has a higher spatial resolution with shorter intervals than with PET, which allows a better discrimination between activation related to different components of the cognitive processes (Rosen, 2002). fMRI can be performed on standard MRI machines after a software upgrade (Rosen, 2002).

Technical limitations include sensitivity to hemoglobin concentrations, head motion artifacts from movements as small as 2mm, long scanning times, and loss of image quality near the hippocampus (Rosen, 2002). In addition, the machine itself is quite loud limiting the ability to use auditory stimuli (Rosen, 2002). There are also unresolved issues related to statistical assessment of functional scans (Corkin, 1998). Of course there are also the limitations associated with any MRI: the small enclosed environment can lead to disorientation and claustrophobia and the strong

magnet can dislodge or disrupt implanted electrical equipment. Non-technical limitations include several factors. First AD may not be the only reason for reduced functional activity in older adults. Second those who have severe cognitive impairment may not be able to comply with the cognitive tasks; this limits the testing to those with less severe disease (Rosen, 2002). In addition, the use of physical tasks – especially those that involve head movement such as speaking – is limited by sensitivity to motion artifact (Rosen, 2002).

Magnetic Resonance Spectroscopy (MRS)

MRS uses technology similar to standard MRI but is able to detect the concentration and synthesis rates of several metabolites including N-acetyl aspartate (NAA), myoinositol (ML), choline, GABA, and glutamate (Felber, 2002; Ricci, 1998). NAA, which is frequently reported as an NAA:Creatinine ratio, is presumed to represent neuron integrity while ML is thought to reflect glial cell integrity (Felber, 2002). Choline and ML represent membrane turnover (Felber, 2002). Standard MRIs convert "molecular moments" derived from active nuclei into 3-D images. MRS takes it one step further by taking advantage of the fact that the resonance frequency created by these molecular moments is affected not only by the

force of the magnetic field but also by the chemical environment (called chemical shift) (Burn, 2003). Thus it is able to detect the presence of each of these chemicals individually by their signature effects upon the molecular moments. Since the naturally occurring ^{13}C is an "MRS active" substance, it can be followed from transport in the blood all the way through its incorporation into GABA, glutamine, or glutamate by GABAergic neurons, glutamatergic neurons, and glial cells, respectively (Burn, 2003). By doing so MRS can be used to visualize the metabolic activity of each cell type in a particular anatomical area (Burn, 2003).

MRS can be performed as photon MRS (1H-MRS) using single-voxel MRS or as multisection proton MRS (MRSI) (Burn, 2003). MRSI allows the acquisition of higher resolution 1cm slices (Burn, 2003). MRSI is just now being used in research and currently there is very little evidence supporting its use. Using 1H-MRS, there is some evidence that in AD there is a relatively greater loss of NAA in the temporal lobe than in the brain as a whole while ML levels may be elevated. This ML elevation may be seen early, in the pre-dementia stage of AD, at least in patients with Down's syndrome (Felber, 2002; Ricci, 1998). An MRSI study showed that there

were significant changes in the NAA/choline and choline/creatinine ratios in the posterior gray matter of AD patients (Felber, 2002; Ricci, 1998).

No radiotracer makes it relatively safe for repeated imaging (Burn, 2003). It also requires fewer specialized resources than PET. However, MRS, unlike fMRI can only be performed using passive brain stimulation (Rosen, 2002). Long scanning times (about 35 minutes) limit its usefulness. It has a relatively low spatial resolution, and only detects compounds with concentrations > 100uM so it is unable to detect most neurotransmitters (Wagner, 2000). Other problems relate to those of MRI generally: small spaces and interactions with metal implants.

3.3. Methods

3.3.1 Classification system used to guide article selection

The Medicare Coverage Advisory Committee (MCAC) report on "Recommendations for Evaluating Effectiveness; Executive Committee Working Group Medicare Coverage Policy" (Executive Committee Working Group, 2001) developed recommendations for evaluating evidence. Although the preference is for direct evidence, few studies directly measure

the effect of diagnostic tests on health outcomes. Studies of these tests typically focus on technical feasibility or operating characteristics.

According to the MCAC assessment criteria, the studies most useful for assessing new technologies are Category 2 or higher using the classification system developed by Fryback and Thornbury (1991), since Category 1 articles relate to technologies that are under development rather than routinely used in clinical practice. Category 1 articles include those that do not pre-specify an *a priori* cutpoint for considering a test result as positive or negative. In order for the results obtained from a given technology to be reproducible across different settings and populations, commonly accepted criteria for determining which patients have a positive or negative test result are needed. Studies that do not pre-specify a cut-point are therefore considered technical feasibility studies rather than diagnostic accuracy studies.

In order to focus our review on articles that would be most informative, we eliminated articles that were clearly technical feasibility studies (Category 1) based on a review of the abstracts. Articles that were identified as potentially Category 2 or higher were then included for full text

review. The majority of these studies lacked of an *a priori* cutpoint and are thus Category 1 articles. Less than a handful of articles were Category 2 and none were Category 3 or higher (refer to Table 1 for details).

For the purpose of this assessment, we chose to include articles that were not only Category 2 or higher, but also Category 1 articles that reported sufficient patient level data to permit the assessment of test operating characteristics if an *a priori* cut point were defined. To provide a more complete picture of the scope of available research studies, we list and briefly describe Category 1 articles that compare test results in aggregate (e.g., mean result for patients with different forms of dementia).

All studies identified for full text reviewed were also examined to determine if the study included design features that are considered hallmarks of a well-conducted study, based on commonly accepted criteria for obtaining unbiased estimates of sensitivity and specificity (Rothman and Greenland, 1998). The criteria were as follows:

1) Consecutive enrollment or random selection of patients for enrollment into the study. Either of these methods can be used to ensure that the types of patients who are enrolled into the

study are similar to those who aren't. Patient selection in this manner allows for generalizing the findings of the study to the population from which the patients arose

2) Randomized, controlled trial design. This study design, in which patients are randomized to receive either the technology of interest (SPECT, Volumetric CT/MRI, fMRI, MRS) or another technology (such as FDG-PET) or clinical assessment, is considered the optimal design for reducing the possibility of differences between the two groups that may explain differences in test performance

3) Matching or adjustment. Two other options for achieving comparability between two or more groups under study are the use of matching or adjusting for differences between the groups during the analysis. Either reduces the possibility of confounding due to differences in patient characteristics (sex, age, distribution of underlying disease) that may result in biased estimates of test accuracy

4) Availability of a clinical exam result, histology or long-term follow-up information on all patients to determine disease status. In order to determine the true disease status for all

patients, an independent gold standard is usually needed. Usually, histology or followup information is considered appropriate for determining true disease status. However, since many of the studies we reviewed were conducted using a cross section design, we relaxed this criterion and included information from a clinic exam as evidence of disease

5) Blinding of the radiologist to disease status. Ideally the test results for the technology should be obtained blinded to clinical information, histology or long-term follow-up results. Determining test positivity unblinded to one or more test results may result in biased estimates of sensitivity for a given test than would be obtained if the radiologist was blinded to the patients' true disease status

6) Use of an *a priori* cutpoint. As discussed earlier, we specifically looked for information regarding use of a pre-determined cut-point in order to classify patients as positive or negative for disease. We used this information to categorize articles as Category 2 using the Fryback et al classification system

7) Patient level data available for articles with no *a priori* cutpoint. We distinguished these articles from other Category 1 articles

under the assumption that these may provide useful information for informing the choice of a cutpoint, were one to be available.

3.3.2 Literature review

3.3.2.1 Literature identification

An OVID search of the MEDLINE database was conducted on February 9th, 2004. Filters and limitations were used to eliminate inappropriate publications. General inclusion criteria were included to maximize the applicability of the search results to the specific questions. The search used applicable MeSH headings and text words with appropriate Boolean operators. After filtering irrelevant publication types, the search resulted in 472 citations for download and screening. Individual review of the abstracts resulted in 55 citations identified for complete article review. Upon initial full-text review, 11 studies were found to have less than 12 patients per study group, 16 studies were of AD patients only, and 6 studies were found to be irrelevant, leaving 22 studies to be reviewed in detail. Six additional articles were identified based on review of references and expert opinions.

3.3.2.2. Search strategy used for identifying abstracts

The following search illustrates the search strategy used for CT.

Refer to Appendix B for additional search strategies.

Ovid Technologies, Inc. Email Service

Search for: from 32 [limit 31 to yr=2001-2004] keep 1-23
Citations: 1-23

Database: Ovid MEDLINE(R) <1966 to January Week 2 2004>
Search Strategy:
---
1 exp *alzheimer disease/di, ra (2628)
2 exp tomography, emission-computed/ (32817)
3 and/1-2 (191)
4 fdg-pet.mp. (2168)
5 1 and 4 (6)
6 or/3,5 (191)
7 limit 6 to yr=2001-2004 (58)
8 6 not 7 (133)
9 pet.tw. (16130)
10 fdg-pet.tw. (2168)
11 exp alzheimer disease/ (31124)
12 exp "sensitivity and specificity"/ (150395)
13 or/2,4,9-10 (38111)
14 or/1,11 (31124)
15 and/13-14 (1197)
16 12 and 15 (111)
17 6 or 16 (274)
18 limit 17 to human (270)
19 limit 18 to english language (229)
20 discriminant analysis/ (3406)
21 20 and 15 (13)
22 risk factors/ (227937)
23 22 and 15 (34)
24 case control studies/ (53037)
25 24 and 15 (61)

26 Diagnosis, differential/ (239899)
27 26 and 15 (146)
28 or/21,23,25,27 (236)
29 28 not 17 (150)
30 limit 29 to human (150)
31 limit 30 to english language (130)
32 limit 31 to yr=2001-2004 (23)
33 from 32 keep 1-23 (23)
34 from 33 keep 1-23 (23)

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3.3.3. Literature selection

3.3.3.1 General inclusion/exclusion criteria for identifying abstracts

Two levels of inclusion criteria were used for including studies. The first level consisted of general criteria applied during the initial literature search:

- English language articles reporting primary data and published in a peer review journal (not abstracts)
- Studies that include at least 12 human subjects (not animal studies) with the condition(s) of interest and technology of interest

A second level of inclusion consisting of a single criterion was applied to all articles initially identified for review. As described previously, if, based on a review of the abstract, an article was determined to be a Category 1

article it was excluded. As a result, 12 articles for SPECT, 9 for Volumetric CT/MRI, 2 for fMRI, and 4 for MRS were identified for full text review.

3.3.3.2. Annotation of full text articles

Data on the enrollment (consecutive or random), study design (RCT), matching or adjustment, use of a defined reference standard and blinding of the radiologist to disease status were obtained on all studies identified for full text review. In addition, we noted whether an *a priori* cutpoint was provided. [As mentioned above, the majority of articles describing test performance did not include the use of an *a priori* cut-point and were therefore considered to be Category 1 articles rather than Category 2]. To provide CMS with information that may be potentially useful for determining an appropriate cut-point, we distinguished Category 1 articles that included patient level data (either listed in Tabular form or presented in a Figure) from those that did not; these two sorts of studies are presented separately.

Each article was reviewed by at least two reviewers. Discrepancies between reviewers were resolved by consensus.

3.4. Results

The results of the literature review are presented below, categorized by question addressed (diagnosis, prognosis, or response to treatment), and subcategorized by Fryback (Category 2 or higher, Category 1 with and without patient level data). Within each Fryback Category, articles are grouped by technology (SPECT, Volumetric CT/MRI, fMRI, MRS). For each article, the annotation includes the aim of the study, the device(s) used, the patient population examined, and a summary of the results. For articles that were Category 1 but did not provide detailed patient level information, we provide a summary statement of the aim of the study only. Details of these studies in terms of their design and conduct are also summarized in Tables 2 through 6.

3.4.1. Studies on the use of the technology to discriminate between Alzheimer's dementia and other causes of cognitive impairment.

3.4.1.1. Category 2 studies

Table 2. Diagnostic Category 2 studies

Author	Enrollment (consecutive or random)	RCT	Comparability (matching or adjusted)	Defined reference standard	Radiologist blinded to clinical info	A priori criteria for test +/-	If a priori criteria were available could 2x2 table be made
SPECT							
Pavics L, Grunwald F, Reichmann K, et al (1999)	No	No	No	Yes	Yes	Yes	Yes
Miller BL, Ikonte C, Ponton M, et al (1997)	Yes	No	Yes	Yes	Yes	Yes	Yes
Jobst KA, Barnetson LPD, Shepstone BJ (1995)	Yes	No	No	Yes	Yes	Yes	Yes

SPECT

Pavics et al. (1999) examined the use of SPECT with Tc HmPAO along with the acetazolamide test in differentiating patients with AD from those with vascular dementia (VD). The authors theorized that the addition of acetazolamide test would aide in distinguishing patients with VD because these patients usually exhibit alterations in the cerebral vasculature. When acetazolamide is administered to normal patients, a generalized and relatively uniform increase in total brain blood flow is usually seen. However, when vascular lesions are present, acetazolamide is unable to cause an increase in blood flow, and areas with impaired

vascular reserve capacity can be visualized when acetazolamide is used in conjunction with SPECT.

Patients with AD were diagnosed using NINCDS-ADRDA criteria; VD was assessed using criteria by Chui et al. DSI Ceraspect and ADAC Genesys systems were used to obtain SPECT images. SPECT images were categorized using Holman criteria (A: normal; B: bilateral posterior temporal and/or parietal cortex defects; C: bilateral posterior temporal and/or parietal defects with additional defects; D: unilateral posterior temporal and/or parietal cortex defects with and without additional defects; E: frontal cortex defects only; F: other large (>7cm) defects and G: multiple small (<7cm) defects)). Data sets were classified as abnormal based on the cortical activity of <60% of the maximum activity. A decreased or unchanged regional hypoperfusion after acetazolamide was defined as a preserved vascular reserve. An increase in hypoperfusion was diagnosed as an impaired vascular reserve capacity. The differences in perfusion patterns between patients with VD and those with AD were statistically significant. Of the VD patients with hypoperfusion, 57% were quantitatively determined to have a decreased vascular reserve capacity compared to

27% of AD patients, suggesting that use of the acetazolamide test with SPECT may be useful in differentiating VD from AD.

Miller et al. (1997) examined the Lund-Manchester criteria (LMRC) for frontal temporal dementia (FTD) in 30 patients diagnosed as having FTD using SPECT. Thirty patients with AD were also included in the analysis for comparison. Details of the SPECT device used in the study were not presented. VD was diagnosed if patients showed bilateral or unilateral anterior frontal or temporal hypoperfusion was present and more severe in the anterior frontal or temporal areas than in the posterior temporal-parietal regions. SPECT was defined as unilateral if Tc HMPAO showed <63% maximal uptake in the anterior temporal and frontal lobe on one side only and bilateral if both sides showed <63% maximal uptake. FTD was confirmed using autopsy results for 11 patients. AD was diagnosed using bilateral posterior parietal lobe hypoperfusion on SPECT and patients had to meet the NINCDS-ADRDA criteria for probable AD. Discriminant analysis was used to identify items from the LMRC that could differentiate between AD and FTD patients. Loss of personal awareness, hyperorality, stereotyped and perseverative behavior, progressive reduction

of speech and persevered spatial orientation were shown to differentiate 100% of FTD and AD patients.

Jobst et al. (1995) examined the use of SPECT with Tc HmPAO and CT in differentiating 118 consecutively enrolled patients with medial temporal lobe dementias, including patients eventually diagnosed with AD (n=80) on histopathology;105 controls were included for comparison. Clinical diagnoses were made using the DSM III and NINCDS-ADRDA criteria. CT scans were obtained using a Siemens Somatom DR1 and ART. A scan was considered positive for atrophy if MTL thickness was $<5^{th}$ centile for controls. SPECT was conducted using a General Electric 400 XCT camera. Cerebral blood flow was assessed and graded visually by consensus using a 4 point scale, with 0 representing normal perfusion, 1=mild perfusion deficit, 2=moderate deficit and 3=severe deficit. Scores of $\geq$ 2 were considered evidence for hypoperfusion. Patients were followed with annual scans and physical exams until they died. Neuropathological exams were performed on patients and AD confirmed using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria. CT alone was shown to have 85% sensitivity and 78% specificity for detection of MTL atrophy. SPECT alone was shown to have 89% sensitivity and 80%

specificity for MTL atrophy; both were shown to have 80% sensitivity and 93% specificity. In contrast NINCDS-ADRDA criteria were shown to be 49% sensitive and 100% specific using probable AD, 93% sensitive and 61% specific using possible AD and 96% sensitive and 61% specific using both.

Volumetric CT/MRI

No studies were included for these technologies in Category 2.

fMRI

No studies were included for this technology in Category 2.

MRS

No studies were included for this technology in Category 2.

3.4.1.2. Category 1 - No *a priori* cutpoint, but patient level data available

Table 3. Diagnostic category 1 studies, with patient data

Author	Enrollment (consecutive or random)	RCT	Comparability (matching or adjusted)	Defined reference standard	Radiologist blinded to clinical info	A priori criteria for test +/-	If a priori criteria were available could 2x2 table be made
SPECT							
Charpentier P, Lavenu I, Defebvre L, et al (2000)	No	No	No	Yes	NR	No	Yes
Defebvre LJ, Leduc V, Duhamel A, et al (1999)	No	No	No	Yes	NR	No	Yes
Steinling M, Defebvre L, Duhamel A, et al (2001)	Yes	No	No	Yes	NR	No	Yes
Walker Z, Costa DC, Janssen AG, et al (1997)	No	No	Yes	Yes	NR	No	Yes
Talbot PR, Snowden JS, Lloyd JJ, et al (1995)	No	No	Yes	Yes	NR	No	Yes
Volumetric CT/ MRI							
Maunoury C, Michot JL, Caillet H, et al (1996)	No	No	No	Yes	Yes	No	Yes

SPECT

Charpentier et al. (2000) examined the use of SPECT with Tc HmPAO in differentiating patients with AD (n=20) from 20 patients with FTD. Patients were selected from a Memory Clinic Center and disease was confirmed using the Lund and Manchester criteria for FTD and NINCDS-ADRDA criteria for patients with AD. Details regarding the type of device were not presented. Discriminant analysis was used to determine a decision rule for distinguishing the two groups of patients using the MMSE and 10 pairs (20) regions of interest in the brain. A score was developed

using five ROI's and the MMSE score that, when applied, identified 100% of the patients with FTD and 90% of the patients with AD. The equation used is as follows:

S=6.1 x (R MedFr) – 9.8 x (MMSE/100)-12.3 x (Ltemp-Par-Occ) + .6 x (L Lat-fr) + 9.6 x (Ltemp-Par) - 9.1

Defebvre et al. (1999) examined the use of SPECT with Tc HmPAO in differentiating dementia with Lewy Bodies (DLB) (n=20), AD (n=20) and Parkinson's Disease (PD) (n=20). SPECT was performed with a brain dedicated, fast-rotating SPECT system, the Tomomatic 564 (Medimatic, Copenhagen, Denmark). Patients with DLB were diagnosed according to consensus guidelines (not specified), patients with IPD were diagnosed based on the United Kingdom Parkinson's Disease Society brain bank criteria and patients with AD were diagnosed using NINCDS-ADRDA criteria. Discriminant analysis was used to determine a decision rule for distinguishing the three groups of patients using the MMSE and 10 regions of interest in the brain. Two scores were developed using seven ROI's (left medial frontal, left lateral frontal, left posterior frontal, left temporoparietal, left parietal and left parietooccipital) and the MMSE score that, when

applied identified 90% of the patients with DLB, 80% of the patients with AD and 95% of the PD patients.

In the same group of patients, **Steinling et al. (2001)** used discriminant analysis to determine a decision rule for distinguishing the three groups of patients (DLB; AD; PD). Fixation values <80% for the tracer were considered significant and values between 80% and 82.5% were considered borderline for identifying ROIs for each dementia type. Using the 10 pairs of ROIs, under the assumption that use of all areas was more informative than those identified using discriminant analysis, led to a correct classification of 87% (52) of the 60 patients. Ninety-five percent of LBD, 90% of FTD and 75% of AD cases were correctly classified using information from all 20 ROIs and MMSE scores.

In DLB, degeneration of nigral neurons with depletion of striatal dopamine occurs, unlike AD, in which significant changes in dopamine have not been observed. Iodine-123 iodobenzamide (IBZM) SPECT can measure post-synaptic dopamine D_2 neuroreceptor availability in the corpus striatum. On this basis, **Walker et al. (1997)** et al. examined the use of IBZM-SPECT in differentiating dementia in patients with DLB (n=20)

from AD (n=13) and normal controls (n=13) using an SME 810 SPECT device (Cygne). Radioactivity ratios in two contiguous slices containing the basal ganglia were calculated for each hemisphere. Patients were recruited from a memory disorders clinic; those with DLB were diagnosed according to consensus guidelines developed by McKeith et al. and patients with AD were diagnosed using NINCDS-ADRDA criteria. Patients with DLB had a significantly lower left caudate/putamen ratios compared to either AD patients or normal controls, and significantly lower right caudate/putamen ratios than controls, suggesting that patients with DLB have changes in striatal post-synaptic D_2 receptors that may be useful for differential diagnosis.

Talbot et al. (1995) examined the use of SPECT with Tc HmPAO in patients with AD (n=30) from patients with non-AD lobar atrophy (n=28) including 15 patients, 5 patients with progressive nonfluent aphasia and 7 patients with semantic dementia. Details regarding criteria used for diagnosing patients were not presented; CT scans were used to confirm lobar atrophy. SPECT was performed using a Toshiba GCA-901A/SA integrated digital camera and computer system. Regional cerebral blood flow (rCBFi) indices were obtained for 31 regions of interest. Principal

component analysis was used to select rCBFi values that could be used to distinguish between the groups of patients. The analysis showed that 86.5% of the variation between patients and normal controls in the original rCBFi data could be explained by 3 components: average rCBFi value, anterior-posterior asymmetry, and left-right asymmetry.

Volumetric CT/MRI

No studies of CT were identified in this group (Category 1 with patient level data.)

Maunoury et al (1996) examined the use of MRI for determining temporal amygdala atrophy in patients with AD (n=21) compared to 14 patients with mixed dementias (3 with vascular dementia, 5 with Parkinson's disease, 5 with Korsakoff's syndrome and 1 with progressive supranuclear palsy) and 15 age-matched controls. Patients with AD were diagnosed using NINCDS-ADRDA criteria; details regarding the diagnoses for the non-AD patients were not presented. MRI was performed using a 1.5-tesla superconducting system (Signa, General Electric, Milwaukee, USA). Compared to patients with other dementias and controls, AD

patients had cerebral atrophy, particularly in the temporal lobes with fissure widening and temporal horn dilatation. The mean temporal amygdala volumes were 726.0 ± 168.4 mm^3 for the AD group, 1, 266.5 ± 390.3 mm^3 for the other types of dementia group and 1240.0 ± 238.2 mm^3 for the control group. Normalized temporal amygdala volumes (obtained by dividing the mean temporal amygdala volume by the mid-sagittal intracranial area) were significantly different for the three groups and were 5.42 ± 1.51; 8.99± 2.74 and 9.25 ± 1.84 for AD, other dementias and the control groups respectively.

fMRI

No studies were identified in this group (Category 1 with patient level data.)

MRS

No studies were identified in this group (Category 1 with patient level data.)

3.4.1.3. Category 1 - No *a priori* cutpoint and no patient level data available

All studies in this group related to aggregate test results in cohorts of patients with AD vs. other types of dementia.

Table 4. Diagnostic Category 1 studies, without patient data

Author	Enrollment (consecutive or random)	RCT	Comparability (matching or adjusted)	Defined reference standard	Radiologist blinded to clinical info	A priori criteria for test +/-	If a priori criteria were available could 2x2 table be made
SPECT							
Varma AR, Talbot PR, Snowden JS, et al (1997)	Yes	No	Yes	Yes	NR	No	No
Starkstein SE, Sabe L, Vazquez S, et al (1996)	Yes	No	Yes	Yes	Yes	No	No
MRS							
Weiss U, Bacher R, Vonbank H, et al 2003	No	No	Yes	Yes	NR	No	No
Block W, Traber F, Flacke S, et al (2002)	No	No	Yes	Yes	NR	No	No

SPECT

Varma et al. (1997) performed HMPAO SPECT imaging on 20 patients with LBD, 57 with AD and 11 healthy controls to investigate patterns of LBD and the ability of the technology to differentiate AD from LBD.

Starkstien et al. (1996) evaluated 230 patients with HMPAO SPECT results in conjunction with psychiatric interviews and neuropsychological assessments to determine differences between consecutively enrolled

patients with probable vascular dementia (VD) and age, sex and MMSE matched patients with probable AD.

Volumetric CT/MRI

No studies were identified in this group (Category 1 without patient level data.)

fMRI

No studies were identified in this group (Category 1 without patient level data.)

MRS

Weiss et al. (2003) assessed the potential role of MRS in revealing diagnostic reasons for cognitive impairment by retrospectively studying 37 patients with AD, 31 with subcortical VD, and 13 with subjective cognitive impairment (SCI) and determining the technology's ability to differentiate among them.

Block et al. (2002) evaluated 34 patients with AD, 70 with motor neuron disease and 22 healthy controls with MRS to determine the metabolic pattern for each disease.

3.4.2. Studies that predict prognosis, including studies on potential harms and benefits of testing and the "value of knowing"

3.4.2.1. Category 2

No studies were identified for this category.

3.4.2.2. Category 1 - No *a priori* cutpoint, but patient level data available

Table 5. Prognostic Category 1 studies, with patient data

Author	Enrollment (consecutive or random)	RCT	Comparability (matching or adjusted)	Defined reference standard	Radiologist blinded to clinical info	A priori criteria for test +/-	If a priori criteria were available could 2x2 table be made
Volumetric CT/MRI							
Jack CR, Shiung BA, Gunter JL, et al. (2004)	**Yes**	No	Yes	Yes	Yes	No	Yes
Dickerson BC, Goncharova I, Sullivan MP, et al. (2001)	**NR**	No	Yes	Yes	NR	No	Yes
MRS							
Jessen F, Block W, Traber F, et al (2001)	No	No	No	Yes	NR	No	Yes
Doraiswamy PM, Charles HC, Krishman KR. (1998)	No	No	No	Yes	NR	No	Yes

SPECT

No studies were identified in this group (Category 1 with patient level data.)

Volumetric CT/MRI

Jack et al. (2004) used serial MRI measures over a 1 to 5 year period on 55 cognitively normal subjects, 41 patients with MCI and 64 patients with AD to determine annual rates of change in brain volume. Changes in the hippocampus, entorhinal cortex , whole brain and ventricle were assessed and patients were classified as either stable or converters. Patients were imaged at 1.5 T (Signa; General Electric Medical Systems, Milwaukee, WI) using a standardized protocol. All images were read by a research associated blinded to clinical information. Patients were monitored using MMSE and Dementia Rating Scale to determine decline. Memory was assessed using the Auditory Verbal Learning Test – Delayed Recall. Patients who were classified as normal or MCI at baseline were categorized as either stable or converters. Patients who converted to AD were categorized as either slow or fast progressors. All four regions of the brain showed greater atrophy among normal patients who converted to AD than among those who remained stable, and was also greater among fast compared to slow AD progressors. None of the four were significantly associated with an increased likelihood of progression.

Dickerson et al. (2001) used MRI to determine hippocampal and entorhinal atrophy in 34 normal controls, 28 patients with cognitive impairment who did not meet the clinical criteria for dementia, and 16 patients with mild, probably AD. MRI images were obtained using a 1.5 Tesla General Electric Signa scanner. Patients were followed for an average of 39 months to determine progression to AD (criteria for progression not described). Among 23 patients with available data (of 28 with cognitive impairment) 12 converted to AD. Converters differed significantly from non-converters in total entorhinal volume but not hippocampal volume; these findings remained significant after adjustment for age and sex.

fMRI

No studies were identified in this group (Category 1 with patient level data.)

MRS

Jessen et al. (2001) used MRI and 1H-MRS to determine whether reduction of N-acetylaspartate (NAA), as a marker for disturbed neuronal integrity, predicts cognitive decline in 13 patients with AD. In particular, the

authors theorized that a progressive decrease in NAA/creatine (Cr) in the medial temporal lobe or in relation to the central region would mirror cognitive decline in patients with AD, based on a previous, cross sectional study. The devices used for conducting the MRI and MRS studies were not described. Patients were monitored over an average of 21 months (range 16 to 33) using MMSE and ADAS-cog to determine decline. Of note there was no control group included in this study. Reductions in NAA were expressed using NAA/CR ratios. In addition ratios of Choline (Cho) and phosphocreatine/creatine were determined. Neither NAA/Cr nor Cho/Cr ratios in the MTL differed significantly between the first and second exam. NAA/Cr and Cho/Cr also did not differ between the first and second examination in the central region.

Doraiswamy et al. (1998) examined the use of H-MRS with NAA and myo-inositol in predicting cognitive decline in 12 patients with AD. Prior autopsy studies of patients with AD had shown decreased NAA levels and raised myo-inositol levels. Of note, no control group was included in this study. Patients were diagnosed using NINCDS-ADRDA criteria. The device used was not described. Patient were examined at baseline and again in 12 months. Cognitive decline was monitored using MMSE scores.

Mean NAA/Cr ratios and myo-inositol to NAA were calculated for each patient at baseline. Baseline NAA/Cr ratios were inversely correlated with the change in MMSE score from baseline to 12 months ($r=-0.62$, $p<0.03$). Baseline myo-inositol/NAA ratios were found to be inversely correlated with MMSE score at followup ($r=-0.70$, $p<0.011$).

3.4.2.3. Category 1 - No *a priori* cutpoint and no patient level data available

Studies focused primarily on cognitively normal subjects with known risk factors or mildly demented subjects, with the technologies used as a potential determinate of progression to AD.

Table 6. Prognostic Category 1 studies, without patient data

Author	Enrollment (consecutive or random)	RCT	Comparability (matching or adjusted)	Defined reference standard	Radiologist blinded to clinical info	A priori criteria for test +/-	If a priori criteria were available could 2x2 table be made
SPECT							
Nobili F, Koulibaly M, Vitali P, et al (2002)	Yes	No	No	Yes	NR	No	No
Johnson KA, Lopera F, Jones K, et al. (2001)	No	No	No	Yes	NR	No	No
Volumetric CT/MRI							
Grundman M, Sencakova D, Jack CR Jr, et al (2002)	No	Yes	Yes	Yes	Yes	No	No
de Leon MJ, Convit A, Wolf OT, et al (2001)	No	No	Yes	Yes	Yes	No	No
Jack CR, Petersen RC, Xu Y, et al. (2000)	No	No	Yes	Yes	Yes	No	No
Killiany RJ, Gomez-Isla T, Moss M, et al (2000)	No	No	No	Yes	Yes	No	No
Yamaguchi S, Nakagawa T, Arai H, et al (1996)	No	No	No	Yes	Yes	No	No
fMRI							
Bookheimer SY, Strojwas MH, Cohen MS, et al (2000)	No	No	No	Yes	NR	No	No
Smith CD, Andersen AH, Kryscio RJ, et al (1999)	Yes	No	Yes	Yes	Yes	No	No

SPECT

Nobili et al (2002) used SPECT to evaluate brain perfusion changes of 47 mild- to moderate AD patients during AchEI therapy in relation to their cognitive evolution.

Johnson et al (2001) used SPECT to evaluate presenilin 1 associated abnormalities regional cerebral perfusion in 57 members of a large pedigree from Colombia, South America.

Volumetric CT/MRI

No studies of CT were identified in Category 1 without patient level data.

In a study of volumetric MRI, **Grundman et al. (2002)** enrolled 769 subjects with mild cognitive impairment (MCI) to predict cognitive decline to AD by measuring hippocampal atrophy using MRI at baseline, 3 year follow-up and, if applicable, at time of clinical diagnosis of AD.

After conducting baseline MRI-guided FDG-PET evaluations on 144 normal elderly patients, **de Leon et al. (2001)** followed subjects for 36 months (105 with complete follow up) to determine if EC METglu reductions can predict cognitive decline and the involvement of the hippocampus and neocortex.

Killiany et al. (2000) conducted baseline MRI scans on 24 normal persons, 79 subjects with mild dementia, and 16 with mild AD and followed all subjects for 3 years to determine if persons in the prodromal phase of AD could be identified before developing clinically diagnosed dementia using MRI measurements.

Jack et al. (2000) calculated annual rates of hippocampal atrophy (based on at least 3 years of follow-up) using MRI in 58 control subjects, 43 patients with MCI and 29 patients with AD. Study findings from **Jack et al. (1999)** were similar.

Yamaguchi et al. (1996) used MRI to evaluate hippocampal atrophy in 24 patients with AD and 17 cognitively normal elderly subjects. Atrophy was compared with presence of apoE allele to determine interaction.

fMRI

Bookheimer et al. (2000) used fMRI to study patterns of brain activation in subjects who were neurologically normal (30 subjects), had one copy of the APOE allele (16 subjects) or were homozygous for the APOE allele (14 subjects) to determine the relation between brain responses to tasks requiring memory and the genetic risk of AD. 60 subjects.

Smith et al. (1999) used fMRI to compare the cortical activation of 2 groups of cognitively normal women, 14 at high risk for developing AD (at least one first-degree relative and apoE genotyping) and 12 at low risk for developing AD (possessing neither risk factor).

MRS

No studies were identified in Category 1 without patient level data.

3.4.3. C. Studies that predict response to treatment, both positive and adverse effects.

There were no articles identified that addressed this question.

4. REFERENCES

Included Studies

Arnaiz E, Jelic V, Almkvist O, et al. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. Neuroreport 2001;12(4):851-5.

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6. APPENDICES

6.1. Appendix A – Glossary

AAN	American Academy of Neurology
AChE-I	Cholinesterase inhibitor
AD	Alzheimer's disease
AHRQ	Agency for Healthcare Research and Quality
ApoE4	Apolipoprotein E-4
Cho	Choline
CI	Cognitive impairment
cm	Centimeter(s)
CMS	Centers for Medicare and Medicaid Services
Cr	Creatine
CT	Computed tomography
DLB	Dementia with Lewy Bodies
EC	Entorhinal cortex
EPC	Evidence Practice Center
FDG	2-Fluro 2-deoxy D-glucose
fMRI	Functional magnetic resonance imaging
FTD	Frontal temporal dementia
g	Gram(s)

HMPAO	Hexamethylpropylene amine oxime
LMRC	Lund-Manchester criteria
MCI	Mild cognitive impairment
MCAC	Medicare Coverage Advisory Committee
MeSH	Medical Subject Heading
METglu	Glucose metabolism
µg	Microgram(s)
mg	Milligram
ML	Myoinositol
ml	Milliliter(s)
mm^3	Cubic millimeter
MMSE	Mini-mental State Examination
MRI	Magnetic Resonance Imaging
MND	Motor neuron disease
MRS	Magnetic resonance spectroscopy
MTL	Medial temporal lobe
mU	Milliunit(s)
NAA	N-acetylaspartate
ng	Nanogram(s)

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NR	not reported
PCG	Posterior cingulate gyrus
PD	Parkinson's disease
Pdem	Parkinsonian dementia
PET	Positron emission tomography
QALY	Quality adjusted life year
rCBFi	Regional cerebral blood flow
RCT	Randomized controlled trials
ROI	Region of interest
SOW	Statement of work
SCI	Subjective cognitive impairment
SPECT	Single photon emission computed tomography
TA	Technology assessment
Tc HmPAO	Technetium-based HMPAO
VD	Vascular dementia

vs.	Versus
%	Percent

6.2. Appendix B – Literature search results for second question posed by CMS.

Literature search results for SPECT.

Ovid Technologies, Inc. Email Service

Search for: limit 30 to english language
Citations: 1-125
Database: Ovid MEDLINE(R) <1966 to January Week 4 2004>
Search Strategy:
---
1 exp *alzheimer disease/di, ra (2639)
2 exp Tomography,Emission-computed, Single-photon/ (13638)
3 and/1-2 (118)
4 tomography.mp. (92925)
5 1 and 4 (184)
6 or/3,5 (244)
7 limit 6 to yr=1995-2004 (143)
8 6 not 7 (101)
9 single-photon emission-computed tomography.tw. (4725)
10 tomography.tw. (88872)
11 exp alzheimer disease/ (31261)
12 exp "sensitivity and specificity"/ (151518)
13 or/2,4,9-10 (100910)
14 or/1,11 (31261)
15 and/13-14 (1142)
16 12 and 15 (106)
17 6 or 16 (315)
18 limit 17 to human (312)
19 limit 18 to english language (263)
20 discriminant analysis/ (3416)
21 20 and 15 (14)
22 risk factors/ (229013)
23 22 and 15 (32)
24 case control studies/ (53391)
25 24 and 15 (56)
26 Diagnosis, differential/ (240645)
27 26 and 15 (165)

28 or/21,23,25,27 (247)
29 28 not 18 (145)
30 limit 29 to human (145)
31 limit 30 to english language (125)
32 from 31 keep 1-125 (125)

Literature search results for CT.

Ovid Technologies, Inc. Email Service

Search for: limit 30 to english language
Citations: 1-144

Database: Ovid MEDLINE(R) <1966 to January Week 4 2004>
Search Strategy:
---
1 exp *alzheimer disease/di, ra (2639)
2 exp Tomography,Emission-computed/ (32929)
3 and/1-2 (192)
4 tomography.mp. (92925)
5 1 and 4 (184)
6 or/3,5 (279)
7 limit 6 to yr=1995-2004 (163)
8 6 not 7 (116)
9 (computed tomography or CT scan or CAT scan).mp. [mp=title, abstract, name of substance, mesh subject heading] (69856)
10 tomography.tw. (88872)
11 exp alzheimer disease/ (31261)
12 exp "sensitivity and specificity"/ (151518)
13 or/2,4,9-10 (122995)
14 or/1,11 (31261)
15 and/13-14 (1416)
16 12 and 15 (128)
17 6 or 16 (368)
18 limit 17 to human (364)
19 limit 18 to english language (310)
20 discriminate analysis/ (0)
21 20 and 15 (0)
22 risk factors/ (229013)
23 22 and 15 (39)

24 case control studies/ (53391)
25 24 and 15 (67)
26 Diagnosis, differential/ (240645)
27 26 and 15 (193)
28 or/21,23,25,27 (283)
29 28 not 17 (168)
30 limit 29 to human (168)
31 limit 30 to english language (144)
32 from 31 keep 1-144 (144)

Literature search results for MRS

Ovid Technologies, Inc. Email Service

Search for: limit 30 to english language
Citations: 1-102

Database: Ovid MEDLINE(R) <1966 to January Week 4 2004>
Search Strategy:
---
1 exp *alzheimer disease/di, ra (2639)
2 exp Magnetic resonance spectroscopy/ or Magnetic Resonance Imaging/ (209607)
3 and/1-2 (356)
4 spectroscopy.mp. (51927)
5 1 and 4 (31)
6 or/3,5 (359)
7 limit 6 to yr=1995-2004 (259)
8 6 not 7 (100)
9 magnetic resonance spectroscopy.tw. (7565)
10 spectroscopy.tw. (51927)
11 exp alzheimer disease/ (31261)
12 exp "sensitivity and specificity"/ (151518)
13 or/2,4,9-10 (235972)
14 or/1,11 (31261)
15 and/13-14 (1190)
16 12 and 15 (101)
17 6 or 16 (403)
18 limit 17 to human (402)

19 limit 18 to english language (351)
20 discriminant analysis/ (3416)
21 20 and 15 (10)
22 risk factors/ (229013)
23 22 and 15 (44)
24 case control studies/ (53391)
25 24 and 15 (49)
26 Diagnosis, differential/ (240645)
27 26 and 15 (158)
28 or/21,23,25,27 (243)
29 28 not 17 (121)
30 limit 29 to human (121)
31 limit 30 to english language (102)
32 from 31 keep 1-102 (102)

Literature search results for MRI

Ovid Technologies, Inc. Email Service

Search for: from 31 [limit 30 to english language] keep 1-101
Citations: 1-101

Database: Ovid MEDLINE(R) <1966 to January Week 4 2004>
Search Strategy:
---
1 exp *alzheimer disease/di, ra (2639)
2 exp Magnetic Resonance Imaging/ (116854)
3 and/1-2 (324)
4 spectroscopy.mp. (51927)
5 1 and 4 (31)
6 or/3,5 (345)
7 limit 6 to yr=1995-2004 (261)
8 6 not 7 (84)
9 (functional magnetic resonance imaging or functional MRI).tw. (3869)
10 fMRI.tw. (3464)
11 exp alzheimer disease/ (31261)
12 exp "sensitivity and specificity"/ (151518)
13 or/2,4,9-10 (166917)

14 or/1,11 (31261)
15 and/13-14 (1094)
16 12 and 15 (104)
17 6 or 16 (389)
18 limit 17 to human (387)
19 limit 18 to english language (340)
20 discriminant analysis/ (3416)
21 20 and 15 (10)
22 risk factors/ (229013)
23 22 and 15 (44)
24 case control studies/ (53391)
25 24 and 15 (49)
26 Diagnosis, differential/ (240645)
27 26 and 15 (155)
28 or/21,23,25,27 (240)
29 28 not 17 (120)
30 limit 29 to human (120)
31 limit 30 to english language (101)
32 from 31 keep 1-101 (101)
33 from 32 keep 1-101 (101)

6.3. Appendix C – Details of relevant excluded articles

Table 7. Excluded studies – less than 12 patients per group

Author	Enrollment (consecutive or random)	RCT	Comparability (matching or adjusted)	Defined reference standard	Radiologist blinded to clinical info	A priori criteria for test +/-	If a priori criteria were available could 2x2 table be made
SPECT							
Julin P, Lindqvist J, Svensson L, et al (1997)	No	No	Yes	Yes	NR	No	No
Donnemiller E, Heilmann J, Wenning GK, et al (1997)	No	No	No	Yes	Yes	No	Yes
Volumetric CT/MRI							
Fox NC, Crum WR, Scahill RI, et al (2001)	No	No	No	Yes	Yes	No	No
Rose SE, Chen F, Chalk JB, et al (2000)	No	No	No	Yes	NR	No	No
Frisoni GB, Bianchetti A, Trabucchi M, et al (1999)	No	No	No	Yes	NR	No	No
Hanyu H, Sakurai H, Iwamoto T, et al (1998)	No	No	Yes	Yes	Yes	No	No
Fox NC, Freeborough PA, Rossor MN (1996)	No	No	Yes	Yes	NR	No	No
Fox NC, Warrington EK, Stevens JM, et al (1996)	No	No	No	Yes	Yes	No	No
fMRI							
Petrella JR, Lustig C, Bucher LA, et al (2002)	No	No	No	Yes	Yes	No	No
MRS							
Catani M, Piccirilli M, Cherubini A, et al (2003)	No	No	Yes	Yes	NR	No	Yes
Constans JM, Meyerhoff DJ, Gerson J, et al (1995)	No	No	No	Yes	Yes	No	No

Table 8. Excluded studies – Alzheimer's disease patients only

Author	Enrollment (consecutive or random)	RCT	Comparability (matching or adjusted)	Defined reference standard	Radiologist blinded to clinical info	A priori criteria for test +/-	If a priori criteria were available could 2x2 table be made
SPECT							
Herholz K, Schopphoff H, Schmidt M, et al (2002)	No	No	No	Yes	Yes	No	No
Ebmeier KP, Glabus MF, Prentice N, et al (1998)	No	No	No	Yes	NR	No	No
Volumetric CT/MRI							
Bozzali M, Franceschi M, Falini A, et al (2001)	Yes	No	Yes	Yes	NR	No	No
Bozzao A, Floris R, Baviera ME, et al (2001)	Yes	No	Yes	Yes	NR	No	No
De Santi S, de Leon MJ, Rusinek H, et al (2001)	No	No	Yes	Yes	NR	No	No
Kantarci K, Jack CR Jr, Xu YC, et al (2001)	Yes	No	No	Yes	Yes	No	No
Hanyu H, Asano T, Sakurai H, et al (1999)	No	No	Yes	Yes	Yes	No	No
Pantel J, Schroder J, Schad LR, et al (1997)	No	No	Yes	Yes	Yes	No	No
Forstl H, Zerfass R, Geiger-Kabisch C, et al (1995)	No	No	Yes	Yes	NR	No	Yes
fMRI							
Rombouts SA, Barkhof F, Veltman DJ, et al (2000)	Yes	No	Yes	Yes	NR	No	No
MRS							
Chantal S, Labelle M, Bouchard RW, et al (2002)	No	No	Yes	Yes	NR	No	No
Kantarci K, Xu Y, Shiung MM, et al. (2002)	Yes	No	Yes	Yes	Yes	No	No
Antuono PG, Jones JL, Wang Y, et al. (2001)	No	No	Yes	Yes	Yes	No	Yes
Catani M, Cherubini A, Howard R, et al. (2001)	No	No	No	Yes	NR	No	Yes
Huang W, Alexander GE, Chang L, et al. (2001)	No	No	Yes	Yes	NR	No	No
Kantarci K, Jack CR Jr, Xu YC, et al (2000)	No	No	No	Yes	NR	No	Yes