Technology Assessment

Use of Positron Emission Tomography and other neuroimaging techniques in the diagnosis and management of Alzheimer's disease and dementia

December 14, 2001

Prepared for the Agency for Healthcare Research and Quality
Contract No.290-97-0014, Task Order 7

by

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SUMMARY

Objective

To assess the benefits for Positron Emission Tomography (PET) scanning in patients with dementia, in patients with mild cognitive impairment and in asymptomatic patients with a family history of Alzheimer's disease (AD), subsequent to the standard evaluation as described in the American Academy of Neurology (AAN) guidelines. The assessment was done by reviewing the scientific evidence regarding the performance of PET, the natural history of AD, and the treatment efficacy and adverse effects of PET, and by creating a decision model linking testing with treatment and outcome. We have used PET as a prototype for a neuroimaging test; however, the model can be applied to a broad range of neuroimaging modalities and treatments.

Search Strategy

We utilized distinct procedures for identifying literature on the natural history of AD and the effectiveness of treatment for AD versus studies of diagnostic performance of PET using 2-Fluro 2-deoxy D-glucose (FDG-PET). We searched the MEDLINE, CINAHL and the HealthSTAR databases from January 1996 to January 2001 for studies describing the operating characteristics of PET. For articles on the natural history of AD and treatment of AD, we focused on identifying the best quality articles best qualified to inform the decision model's parameter requirements.

Selection Criteria

We identified 15 articles published in peer- reviewed journals and containing original data on more than twelve human subjects relevant to the efficacy of PET in the diagnosis of AD. The reference standard used was either histopathology or clinical diagnosis.

Data Collection and Analysis

Information from these selected studies was used to construct evidence tables. We analyzed the studies by constructing a summary receiver operating characteristic (S-ROC) curve. Test performance, natural history and quality of life studies were used to provide baseline and range estimates for an integrative model. This integrative model was a Markov decision model constructed using DATA 3.5 software (Boston, MA: TreeAge Software, Inc). The decision model was evaluated with regard to individuals presenting with

- dementia (Scenario A)
- mild cognitive impairment (MCI) (Scenario B), and
- no symptoms, but with a first-degree relative with AD (Scenario C).

In addition to a base-case analysis geared to the "typical" individual in the scenario, we performed extensive sensitivity analyses to evaluate the robustness of the baseline conclusions as well as to allow an evaluation of hypothetical scenarios not supported by the current evidence. That is, we recognized that in the future more efficacious

treatments might become available and that these treatments might or might not have greater side effects than the current treatments. Our sensitivity analyses illustrate the impact of such treatments on the results.

Main Results

For patients with mild or moderate dementia, three strategies were considered: (1) to treat all patients with a diagnosis of AD after a standard work-up with anticholinesterases (AChE-I) – “Treat All”, (2) treat only if PET positive – “Test”, and (3) not to test or treat – “No Test/No Treat”. Physical outcomes were measured by life expectancy, quality-adjusted life expectancy, and severe- dementia-free life expectancy. The pooled sensitivity estimate for PET (95% confidence interval) was determined to be 88% (79% to 94%), and a pooled specificity estimate of 87% (77% to 93%) for distinguishing normal healthy controls from patients with AD.

For the baseline case analysis in patients with dementia (Scenario A), the “Treat All” strategy is preferred over the other two in terms of quality-adjusted life years, life expectancy or severe-dementia-free life expectancy. The absolute difference between the strategies is small, but is robust in sensitivity analyses. This implies that although costs were not considered in this assessment, the direction of the conclusions would not change if costs were to be included. The “Test” strategy is preferred only in terms of the measure “percentage correct diagnosis”. When hypothetical treatments are considered, “Test” becomes the more attractive strategy as complications becomes more severe.

But if efficacy is simultaneously increased with dangerous treatment – as it logically should be in order to be worth considering – “Test” becomes less attractive.

For patients with MCI (Scenario B), the evidence for treatment efficacy is assumed to be the same as that for dementia patients since the results of the analysis are virtually the same as for patients with dementia.

For asymptomatic individuals with an elevated risk (Scenario C), the “Treat All” strategy is preferred in the base case, as with the symptomatic scenarios. This approach presumes that treatment is effective in this population. Testing could become preferred for a hypothetical treatment that is highly effective but associated with a risk of severe decrement in quality of life.

Abbreviations Used in the Text

AAN	American Academy of Neurology
Aβ	Beta-amyloid
AChE-I	Cholinesterase inhibitor
AD	Alzheimer's disease
AHRQ	Agency for Healthcare Research and Quality
ApoE4	Apolipoprotein E-4
cc	Cubic centimeter(s)
CDR	Clinical Dementia Rating
CI	Confidence interval
cm	Centimeter(s)
CMS	Centers for Medicare and Medicaid Services
DFLE	Dementia free life expectancy
DSM	Diagnostic and Statistical Manual of the American Psychiatric Association
FDG	2-Fluro 2-deoxy D-glucose
g	Gram(s)
L-DOPA	Levo dopa
LE	Life expectancy
MCI`	Mild cognitive impairment
MCAC	Medicare Coverage Advisory Committee
MeSH	Medical Subject Heading
µg	Microgram(s)
mg	Milligram

ml	Milliliter(s)
MMSE	Mini-mental State Examination
MRI	Magnetic Resonance Imaging
mU	Milliunit(s)
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
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PD	Parkinson's disease
PET	Positron emission tomography
QOL	Quality of life
QALY	Quality adjusted life expectancy
RCT	Randomized controlled trials
ROC	Receiver operating characteristic
RR	Relative risk
SDFLE	Severe dementia -free life expectancy
SPECT	Single photon emission tomography
SROC	Summary receiver operating characteristic
TP	Transition probability
vs.	Versus
%	Percent

INTRODUCTION

Epidemiology

Each year approximately 350,000 individuals manifest Alzheimer's disease (AD) (Brookmeyer, Gray, and Kawas, 1998). The incidence and prevalence of AD climb steadily after age 65 years so that 30-50% of individuals in the eighth to ninth decades have AD (Clark and Trojanowski, 2000).

AD is the most common etiology of dementia, representing approximately two-thirds of cases (Clark and Trojanowski, 2000; Knopman, DeKosky, Cummings, et al., 2001). Other dementias that can clinically present like AD include Lewy Body dementia, frontal lobe dementia, frontotemporal dementia, and vascular dementias. Since people with AD are also more likely to have co-morbidities such as diabetes and atherosclerosis, many people with AD pathology have dementia of mixed etiology.

AD is a complex genetic and environmental disorder (Roses, 1997). Among patients under the age of 65, the etiology of AD is dominated by autosomal dominant inherited mutations of the presenilin or amyloid precursor polypeptide genes (Selkoe, 1998) and polymorphisms of the apolipoprotein E gene (risk factor allele epsilon 4 or ApoE4) (Roses, 1997); together these genetic predispositions occur in 90% of the AD cases in younger individuals (Rubensztein and Easton, 1999). In late onset AD, genetic factors appear less prevalent with perhaps 60% of cases of AD in individuals aged over 65 years having ApoE4 (Rubensztein and Easton, 1999).

AD is a progressive neurodegenerative disease. Initial histological changes may be present in an asymptomatic individual; based on a study of asymptomatic autosomal dominant ApoE4 patients, such subclinical involvement may last for over 10 years (Knopman, DeKosky, Cummings, et al., 2001; Petersen, Stevens, Ganguli, et al., 2001). This is followed by mild cognitive impairment (MCI), which is distinguished from dementia by the absence of functional disability, or by mild dementia, which inexorably progresses through increasing levels of disability. The course of AD is highly variable. While 15% of patients with MCI progress in any given year (Petersen, Stevens, Ganguli, et al., 2001), prolonged plateau periods have been observed (Katzman, 2001). The total duration of clinical illness ranges from 5-25 years.

Diagnosis

In the absence of any established biological marker for the diagnosis of AD or of disease activity, the current standard for diagnosis of AD is based on a clinical evaluation. The clinical evaluation recommended by the American Academy of Neurology (AAN) includes a complete history, physical and neuropsychiatric evaluation and screening laboratory testing (Knopman, DeKosky, Cummings, et al., 2001). They also recommend the use of anatomical neuroimaging in the initial evaluation of dementia. The diagnosis of AD is made when findings are consistent with AD (e.g., the patient has a cognitive disorder typical in type and course as AD and does not have a condition that may mimic AD in the early stages of disease, such as cerebrovascular disease, depression, metabolic disorder, sleep disorder, renal or liver disease, among others). It is not uncommon to have multiple diagnoses with a primary diagnosis of AD

and with other causes of cognitive disorder also present in an individual patient (Clark and Trojanowski,2000; Knopman, DeKosky, Cummings, et al., 2001), especially AD concomitant with vascular dementia. The prevalence of reversible dementia is 18%, but only 1% of cases are resolved entirely with treatment (Walstra, Teunisse, van Gool, et al., 1997).

For most patients with MCI and for some patients with early stages of dementia, diagnosis depends on the observation and documentation on repeat visits of clinical progression through follow-up visits over intervals of one-half to one year. For early or apparently stable cases, this period serves as a time to carry out initial evaluation, to establish neuropsychological baselines for comparison, to identify and treat any other acute or chronic medical condition likely to compromise cognitive or functional ability, and to observe clinically the patient's actual course.

In addition to recommended examinations, other tests have been proposed for the evaluation of individuals who may have AD. Functional neuroimaging is one class of tests that may be useful for this purpose. Two approaches to functional neuroimaging include single-photon emission tomography (SPECT) and positron emission tomography (PET) with markers for cerebral blood flow or glucose metabolism. While neither of these modalities is currently recommended in the routine evaluation of dementia, they may have potential value because they can demonstrate in AD patients the expected anatomical pattern of bilateral hypometabolism in the temporal and parietal lobes (Hoffman, Welsh-Bohmer, Hanson, et al., 2000; Small, Ercoli, Silverman,

et al., 2000). Notably, involvement of the frontal lobes, and some asymmetry in early cases is also observed. PET scans typical of AD can be differentiated clinically by visual inspection from scans suggestive of vascular etiology (asymmetric and focal abnormalities) and scans supportive of frontal lobe or lobar dementias (striking hypometabolism of frontal or temporal lobes with sparing of parietal lobes).

The potential for functional tests to identify individuals at the early stages of their disease is supported by studies of persons who are at increased genetic risk of AD because they bear one or more ApoE4 alleles. Even at ages much earlier than the average age of clinical onset such individuals have reduction of cerebral glucose metabolism corresponding to their grade of genetic risk (Bookheimer, Strojwas, Cohen, et al., 2000; Small, Ercoli, Silverman, et al., 2000). This area has the potential for further developments using the higher resolution of magnetic resonance imaging (MRI)-spectroscopy, with the possible development of specific ligands for AD pathology, particularly amyloid plaques.

Treatment

There is no known treatment to prevent or cure AD. Current therapies are aimed at symptomatic relief and at halting or slowing disease progression. Common treatment strategies include stroke risk reduction, antioxidant therapy (vitamin E), and use of cholinesterase inhibitors (AChE-I) even in prodromal or early stages (Doody, Stevens, Beck, et al., 2001). AChE-I therapy is aimed at correcting the central cholinergic deficit in persons with AD, This therapy has been shown to modestly delay the progression of disease in individuals with mild to moderate dementia (Mohs, Doody, Morris, et al.,

2001), and it may also reduce the rate of institutionalization in patients with more severe dementia (Getsios, Caro, Caro, et al., 2001). Significant adverse events with currently recommended AChE-I therapy are uncommon (Mohs, Doody, Morris, et al., 2001). Approved AChE-I agents include donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl). Multicenter trials of AChE-I in MCI are already being conducted (Morris, Storandt, Miller, et al., 2001) .

Future therapies are aimed at prevention, early treatment, and cure. Human trials of active immunization with β-Amyloid (Aβ) are underway. Aβ is a fibrillar 40-42 amino-acid peptide accumulating in the brains of AD patients and eliciting neuronal cell death (Gurwitz, 2001). Immunization with another Aβ-like peptide has been studied in mice, where reduced burden of the Aβ plaques were observed in the hippocampus and the cortical regions of the brain (Sigurdsson, Scholtzova, Mehta, et al., 2001). Other therapies based on the observation of Apolipoprotein E-4 (ApoE-4) as a genetic risk factor are under active development. These therapies may result in a significant slowing of the disease process of AD. If these therapies prove effective at early or even pre-clinical stages of AD, they will make the current standard diagnostic approach obsolete. The challenge for diagnosis will be not only to identify individuals with disease but also to rule out disease – especially if new therapies have common and significant adverse effects or are exceedingly expensive.

Task Order- Evaluating the Role of PET in Patients who may have Alzheimer's disease

It has been proposed that the tremendous burden of AD could be reduced by improved diagnosis. The Center for Medicare and Medicaid Services (CMS) has received a request for a national coverage decision on the use of Positron Emission Tomography (PET) for the diagnosis and management of Medicare beneficiaries with suspected AD and other dementias linked to old age. CMS referred the request to the Medicare Coverage Advisory Committee (MCAC) and asked the Agency of Healthcare Research and Quality (AHRQ) to review the existing scientific evidence with regard to the demonstrated and potential role of PET in reducing the burden of disease for individuals with possible AD. The Duke Evidence-based Practice Center has been commissioned by AHRQ to produce this report in support of the deliberations of the MCAC Diagnostic Imaging panel.

Evaluation of PET in the Context of MCAC Guidelines.

In determining the effectiveness of new medical products and services (e.g., laboratory tests, diagnostic procedures, treatments, each panel of the MCAC employs certain criteria and procedures to evaluate the adequacy of the evidence and magnitude of clinical benefit. The MCAC Executive Committee has issued general guidance to the panels in the form of suggestions about how to evaluate the adequacy of evidence and the magnitude of benefit (Medicare Coverage Advisory Committee, 2001). This report,

meant to assist in the Diagnostic Imaging panel deliberations, incorporates the following recommendations issued by the Executive Committee.

First, it is necessary to determine whether the scientific evidence is adequate to draw conclusions about the effectiveness of the intervention in routine clinical use in the population of Medicare beneficiaries. Second, the size of health effect produced by the intervention must be evaluated. Evidence from well-designed studies must establish how the effectiveness of the new intervention compares to the effectiveness of established services and medical items.

When evidence is insufficient to draw conclusions about the effectiveness of an intervention, no attempt is made to classify the size of the possible effect. Instead, the reason for the determination of evidence is explained and an opinion is formed about the possibility of developing better evidence and the potential benefits of obtaining better information.

In order to evaluate diagnostic tests, the MCAC applies criteria similar to those used for other health interventions. Two basic questions are asked: (1) is the evidence adequate to determine whether the test provides more accurate diagnostic information? and (2) if the test improves accuracy, is the evidence adequate to determine how the improved accuracy affects health outcomes?

In this context, the task is to focus on the issue of the medical benefit of PET scanning, in addition to a standard evaluation (including a clinical examination and structural

neuroimaging), for individuals who may have AD in comparison with other evaluation strategies that are currently covered by Medicare. As noted in the introduction, the comparator intervention is the clinical evaluation of individuals with cognitive impairment recommended in a guideline produced by the AAN (Knopman, DeKosky, Cummings, et al., 2001). This guideline is summarized in Appendix A.

The strongest support of a clinical benefit for a diagnostic test would be derived from direct evidence from a comprehensive randomized control trial. Such a trial would randomize patients to receive a conventional evaluation or an evaluation that includes the new test, and the primary study measure would be a clinical outcome that corresponds to the health burden of the disease. As detailed in this report, no study of PET in patients who may have AD has provided this level of evidence. Thus the evaluation of PET who may have AD must rely on indirect evidence.

While indirect evidence is less persuasive than direct evidence, it can nonetheless be sufficient for decision-making. Indirect evidence can be used to establish links in a logical or causal chain – in this case between PET use and diagnosis of AD and between diagnosis of AD and clinical outcome. The scientific evidence is evaluated to determine if use of PET leads to more accurate diagnosis of AD and if more accurate diagnosis of AD can (via appropriate treatment) lead to a clinically meaningful benefit.

To provide a fair evaluation of PET for patients who may have AD and to present an analysis that is useful to MCAC and CMS in current and future deliberations, we

focused on the circumstance for which the evidence regarding treatment benefits is strongest – the presence of mild or moderate dementia. We link the evidence through the use of a Markov model. This model provides projections of a variety of important clinical outcomes. Sensitivity analysis is used to examine the robustness of these projections and to identify circumstances under which a new diagnostic test could be particularly attractive (e.g. a diagnostic test that is better than its comparator), or for a treatment that is associated with different levels of benefit and harm.) We extend this analysis to two additional scenarios for which important clinical evidence is either scanty or absent – testing for individuals with mild cognitive impairment, or testing asymptomatic individuals with a family history of AD in a first-degree relative. Here, we provide the CMS with a framework for future deliberations informed by new evidence about testing or treatment.

Summary of Key Questions

The objectives described above were summarized in three key questions corresponding to the three clinical scenarios:

1. Scenario A: In patients with dementia, can PET be used to determine the type of dementia, thus facilitating early treatment of AD and perhaps other dementia subtypes?
2. Scenario B: For patients with MCI, could PET be used to identify a group of patients with a high probability of AD so that they could start early treatment?

3. Scenario C: Is the available evidence enough to justify the use of PET in a group of asymptomatic patients with an elevated risk in view of a family history of AD so that they could start early treatment?

We organized our responses for each key question/scenario into the following sub questions.

1. What are the possible clinical management options and corresponding expected outcomes for the scenario?
2. What is the diagnostic performance of PET in the scenario?
3. What are the benefits and adverse effects of treatment options that might be used in the scenario?
4. For a patient with a given state of cognitive function which strategy is most likely to provide better health outcomes?
5. What are the legal, ethical and psychosocial impacts of receiving a dementia diagnosis for individuals included in the scenario?

METHODOLOGY

The methods and procedures used to develop this report emphasized a comprehensive evaluation of the evidence regarding the operating characteristics of PET and an estimation of inputs required for the model. Because this effort was organized around a decision model, the section begins with the methodology employed for the construction of the model. This is followed by an explanation of our approach to the literature review regarding PET performance, including descriptions of the literature search, MeSH terms used, number and identity of the databases searched, and years included in the search. Finally, we describe the methodologies used to estimate other model inputs, including the probability of disease progression from year to year (transition probabilities) and the efficacy of treatment. By applying varying sensitivities and specificities of PET in our analysis, we have taken into consideration the effect of using any other neuroimaging modalities for diagnostic purposes.

Methodology: Model Construction

Purpose

The model was constructed to address the following question: For a patient with a given state of cognitive function, which strategy is more likely to provide better health outcomes? The specific cognitive states considered were 1) mild or moderate dementia, 2) mild cognitive impairment (MCI), and 3) asymptomatic with a first-degree relative with AD. These states correspond to the 3 key questions noted in the introduction and are

denoted throughout this report as Scenario A, Scenario B, and Scenario C, respectively. The strategies examined were 1) no testing and no treatment, 2) testing with PET and treatment of patients with positive test results and 3) no testing but treatment of all patients. Since age is the dominant factor in the epidemiology of AD we have explicitly incorporated age into the structure of the model. The ages that we have considered for our analyses are 65 to 99 years. The rationale for the management strategies considered will be discussed in the "*Results*" section. All patients were assumed to have completed a standard work-up, as detailed in Appendix A.

Methods

Structure of the Model

For the effectiveness analysis, we constructed a model with two major components. The first component was a 6-state decision model (Figure 1) that simulates the natural history of individuals who may have AD. The second component was an intervention model that represents possible screening/diagnosis and treatment strategies. The model was developed using DATA 3.5 software (Boston, MA: TreeAge Software, Inc). The structural and estimation assumptions made for the purpose of the model are stated in Table 1.

Natural History Component

The model follows a cohort of men and women from age 65 to 99 years. At the beginning of the simulation, all members of the cohort are assumed to be in one of the following states: asymptomatic, but at an elevated risk because of a family history of

AD, MCI or mild or moderate dementia, definitions of these states are provided in Table 2, with details in Appendices B and C. Cycle lengths are one year.

Certain structural and estimation assumptions were made in the model (Table 1). An attempt was made to construct these assumptions to be unbiased for or against testing. When this was not possible, we have chosen assumptions that would favor testing.

For the natural history component of the model, patients can either remain in the same state or progress to a more severe state including severe dementia or death; regression to a less severe state is permitted structurally, but is assumed not to occur. In order to make the model more generic, its structure allows for future treatments that would actually reverse the progress of AD. For all analyses presented here, the probability of such backward transitions has been set to zero. [That is, for the present purposes we assume that any backward transitions observed are a result of measurement error and not a true improvement in state.] Patients who are asymptomatic but are at an elevated risk of developing dementia can either remain in the same state or progress to MCI. Patients who have MCI can either remain in that state or progress to mild dementia. Patients with mild dementia can either remain in the same state or progress to the moderate or severe state. Patients with moderate dementia can either remain in the same state or progress to the severe state. Patients with severe dementia can only remain in the same state or die. Progression rates for patients with mild, moderate or severe dementia depend only on observed symptoms and are not based on underlying AD. All patients are at risk from death from any causes. The states and allowed

transitions of the natural history model are shown in Table 2, the model is in Appendix D. Note that patients are further characterized in the model with regard to their status as true positive (TP), true negative (TN), false positive (FP), or false negative (FN). This denotes the correspondence between the patients' actual diagnosis (AD or no AD) and the diagnosis that would be assigned to them based on clinical and/or test results – the diagnosis that would be used for assigning a treatment.

To be more explicit:

TP = Diseased and treated as having AD

FP = Not diseased and treated as having AD

TN = Not diseased and treated as not having AD

FN = Diseased and treated as not having AD.

Intervention Component

The intervention component of the decision model was constructed to allow a wide range of interventions to be considered including any test with a dichotomous outcome, any treatment that is unconditional or is conditional on either an immediate test result or future health event (i.e., progression to more severe symptoms). Treatments are modeled to have a risk of complications that can consist of any combination of short- and long-term disutility (decrement in quality of life), increase in rate of progression of symptoms, or increase in risk of death.

Measures of Effectiveness

We estimated effectiveness using several measures. First, we calculated life-years saved. This calculation allows comparison with other health interventions and with other (cost-effectiveness) analyses of PET scanning. We also calculated quality-adjusted life-years to account for the morbidity associated with each strategy. Weights for the quality adjustments were derived from the literature and applied to the natural history states and the states that would result from treatment and/or diagnosis using PET scanning (Neumann, Kuntz, Leon, et al., 1999). We estimated the percentage of true positives, false positives, true negatives, false negatives and correct diagnosis (true positives plus true negatives). [As noted above, these categorizations refer to the correspondence between a patient's actual diagnosis (AD or no AD) and the diagnosis that would be assigned based on clinical and/or test results, i.e., the diagnosis that would be used for assigning a treatment. For example, a patient could be a true positive if he or she had AD, had a positive test and is treated, or if he or she is not tested and is treated nonetheless]. We also estimated severe-dementia-free life expectancy (SDFLE) for patients who have mild or moderate dementia and dementia-free life expectancy (DFLE) for patients who have MCI or who are asymptomatic but have an elevated risk of AD.

Model Validation

The structure of the model was validated by asking various clinical experts to review its states, treatments, focus, and level of detail. The parameter inputs of the model were derived by the above literature review process and also presented to experts for additional review. The software implementation of the model was assessed

(1) by noting that the relative impact of each of the factors in the one-way sensitivity analyses was in the anticipated direction and (2) by developing various extreme scenarios (e.g. test with 100% sensitivity and 100% specificity) and checking that the anticipated strategy was in fact preferred.

Analysis

Base case analysis: For each scenario, we performed a base case analysis using the best available estimates for model inputs (Table 3).

One-way sensitivity analyses: We performed one-way sensitivity analysis by varying each model input over its plausible range (Table 3), keeping all other variables at their base case values.

Hypothetical treatment analyses: As it was evident from the onset that diagnostic tests can be particularly valuable when treatments are effective, but have significant adverse effects, we examined the impact of treatment complications on projected outcomes and preferred strategy. We considered several hypothetical treatments characterized by a variety of qualities. These include a treatment with long-term effects manifest as either a prolonged decrement in utility (50% reduction in utility for 1 year or 20% reduction in utility for a lifetime), an increase in rate of progression of disease (relative risk for progression of 2 for 1 year), or an increase in the mortality rate (relative risk for death of 5 for 1 year).

Methodology: Literature Search

The literature search had two goals: 1) to identify all relevant clinical studies using 2-Fluro 2-deoxy D-glucose PET (FDG-PET) for diagnosis of AD and 2) to provide parameter estimates for the decision model. We utilized distinct procedures for identifying literature pertaining to these two goals. The methods for identifying and evaluating the FDG-PET literature are discussed in detail below. To identify parameter estimates that were needed for the decision model, specifically, estimates related to natural history of AD and the efficacy and adverse effects of treatment of AD, we focused on identifying existing systematic reviews, meta-analyses, or independent studies. In addition to referring to literature on previous decision models, we sought recommendations for high-quality studies from our local and consultant experts.

Article identification

The comprehensive review of the literature was a multi-step process, identification of databases, abstraction of individual articles into the evidence tables, and the subsequent meta-analysis.

To identify articles pertaining to the characteristics of FDG-PE, we performed a comprehensive literature search. We worked through several iterations of the search strategies and excluded as many non-relevant articles as possible without jeopardizing the inclusion of relevant articles. The search strategy combined the concepts of "Alzheimer's disease" and "positron emission tomography" and was limited to articles in

English and on human subjects. In consideration of the advances in technology in recent years, we limited our search to articles published between the years 1995 and 2001. For the PET concept, we used the Medical Subject Heading (MeSH) term " tomography, emission computed" and text word searches for "PET" and "FDG-PET". To select articles with data on diagnostic performance of PET, we used the MeSH heading "sensitivity and specificity." This strategy for MEDLINE elicited 162 articles.

Because this set of citations failed to include several articles known to us from a previous systematic review on this topic (Adams and Flynn, 1998), we then revised the search strategy by examining the indexing terms of the missed citations. We broadened our strategy to include the additional MeSH words "discriminant analysis", "risk factors", "case-control studies", and "differential diagnosis" (Table 4). This search yielded 113 additional articles from MEDLINE for a total of 275 articles. We repeated the same process for CINAHL and HEALTHSTAR and identified an additional 7 citations.

Two reviewers – a methodological expert and a content expert – reviewed the abstracts of all the articles. At least one of the two reviewers selected 108 of the abstracts. Full text versions of these articles were then obtained. References from these articles were also examined, and pertinent ones acquired. The database finally had 320 articles.

Selection Process

The criteria used to select an article for systematic review are detailed in Table 5.

Data Abstraction Process: Of the 320 citations reviewed, 42 were selected for a full-text review and abstraction (Appendix E). Two experts reviewed each of these 42 articles. Based on the inclusion criteria, 18 (43%) were included in the final review.

A quality score was also developed at this stage based on eight criteria that were considered relevant to the current analysis (Table 6). For each of the eight criteria, a score or zero of 1 was assigned: a score of 0 was assigned if the paper did not adequately meet the criterion or if the data were inadequate to determine the criterion, and a score of 1 was assigned if the paper met the criterion. The scores for all eight criteria were summed to give a final score for the study.

Two members of the project independently abstracted each study. They created a two-by-two table and extracted the key data that permitted calculation of sensitivity and specificity for use in analyzing the operating characteristics of the test. All the two-by-two table data were entered into a computer database, and data from the two members of each reviewing team were compared and reconciled. The entire process of literature search is summarized in Table 7.

The evidence table entries were created by one member of the team and were over-read by another member, and then revised. Fifteen articles included studies comparing AD patients with normal controls, and three studies compared AD and non-AD

dementias. These 18 studies (43%) were further abstracted into evidence tables (Evidence Table 1).

Meta-Analysis

Meta-analyses were performed to quantify the diagnostic performance and clinical impact of PET. The meta-analysis of PET diagnostic performance involved two technologies: (1) Summary Receiver Operating Characteristic (S-ROC) curve analysis and (2) Separately averaged sensitivity and specificity values across studies.

The S-ROC method assumes that the variability in the reported sensitivity and specificity values from different studies is due to different cutoff values being applied (Moses, Shapiro, and Littenberg, 1993) Each study provides a pair of sensitivity and specificity values to the analysis. It uses a regression method to fit a curve that best describes the data in the Receiver Operating Characteristic (ROC) space. We used the unweighted S-ROC method because it is considered less biased than the weighted regression method (Irwig, Macaskill, Glasziou, et al., 1995).

If multiple thresholds are available for individual diagnostic test studies, ROC curves can be constructed, and the areas under the curves can be estimated. The area under the curve provides an assessment of the overall accuracy of the test and allows comparisons with other tests.

However, the range of sensitivity and specificity values from studies in a meta-analysis of diagnostic tests is often limited, and extrapolation of the S-ROC analysis beyond the values of actual data is not reliable. When there is little variability in the test results – when studies appear to be operating at similar thresholds and report similar results – S-ROC analysis provides little additional information. In this case, separately averaged sensitivity and specificity values across studies will give similarly useful summary information.

We combined the sensitivity and specificity values of the tests across studies using a random effects model to estimate the average values. A random effects model incorporates both the within-study variation (sampling error) and between-study variation (true differences in discrimination) into the overall diagnostic performance estimates. The random effects model is conservative in the sense that it gives a wider confidence interval than the fixed effects model (which considers only within-study variability) when estimates are based on heterogeneous results.

When each result is combined separately, sensitivity and specificity tend to underestimate the true test sensitivity and specificity. They are nonetheless useful estimates of the average test performance and provide an indication of the approximate test operating point for most of the studies. Inspecting the location of the combined estimates and noting the distance of the combined estimates from the S-ROC curve can verify the appropriateness of this method. In our experience, the random effects-averaged sensitivity and specificity results are close to the unweighted S-ROC curve

and well within the confidence intervals of each other. Average sensitivity and specificity results also serve as useful baseline test performance values for the decision and cost-effectiveness analysis (Lau, Balk, et al.,2001).

Statistical analyses using the S-ROC curve method and combining sensitivity and specificity using the random effects model were performed using the "Meta-Test" version 0.6. This computer program has been developed by Dr. Lau and is available to the public. We report 95 percent confidence intervals with all estimates.

Methodology: Estimation of Inputs

In addition to estimating test sensitivity and specificity, our model required estimates of transition probabilities and treatment efficacy. Below we describe the steps taken to obtain these estimates, including the assumptions required.

Transition Probabilities

It should be noted that our model requires age-specific probabilities of transitions between various states. However, based on the opinion of our experts in Alzheimer's disease, no data set contains this information to the level of precision we require (including the otherwise excellent CERAD study). Accordingly, we have derived a method that combines various items of information available from the literature (e.g., overall population-based death rates by age but not state, transition probabilities by state but not age, etc.). Our approach involves first estimating transition probabilities for patients with AD, then estimating transition probabilities for those without AD.

Step 1: Estimate age-specific annual mortality rate of patients with AD.

Age specific annual mortality rate of patients with AD were calculated using a US population life-table of annual mortality rates by age, an estimate of the prevalence of AD by age, and a risk ratio of death for patients with AD compared to patients without AD. We denote the age-specific mortality rate by μ_{age}, the prevalence of AD as p (AD), the relative risk of death for patients with AD as $RR_{AD \rightarrow D}$, and the age-specific mortality rate for patients without AD as $\mu^{no\ AD}_{age}$, we obtain the age-specific annual mortality rate for patients without AD by solving for $\mu^{no\ AD}_{age}$. The age-specific annual mortality rate for patients with AD is

$$\mu^{AD}_{age} = (RR_{AD \rightarrow D})(\mu^{no\ AD}_{age}), \text{ where}$$

$$\mu^{no\ AD}_{age} = \mu_{age}/[(p\ (AD)\ (RR_{AD \rightarrow D})+(1-p(AD))], \text{ derived from the relationship}$$

$$\mu_{age} = (1-p(AD))\ (\mu^{no\ AD}_{age}) + (p(AD))\ (RR_{AD \rightarrow D})\ (\mu^{no\ AD}_{age})$$

This calculation assumes that the RR of death due to AD is the same for all ages.

Step 2: Estimate the age-specific mortality rates (i.e., transitions to death) for AD patients in the mild, moderate, and severe symptom categories.

Using the above age-specific mortality rate for patients with AD, an estimate of the relative prevalence of symptoms for patients with dementia, the relative risk of death for patients with AD having moderate symptoms in comparison with patients having mild symptoms, and the relative risk of death for patients with AD having severe symptoms in comparison to those having mild symptoms, estimate the age- and symptom-specific mortality rates.

For a specific age group of patients with AD, we denote the overall mortality rate as μ^{AD}_{age}, the prevalence of mild, moderate, and severe symptoms as p_1, p_2 and p_3 ($p_1+p_2+p_3=1$), and the relative risk of moderate versus mild symptoms and the relative risk of severe versus mild symptoms as R_{21} and R_{31}, respectively. Then, the age-specific annual mortality rate for patients with mild symptoms, μ_{age}, solves

$$\mu^{AD}_{age} = (p_1)(\mu_{age}) + (p_2)(R_{21})(\mu_{age}) + (p_3)(R_{31})(\mu_{age})$$

The age-specific annual mortality rates for patients with moderate and severe symptoms are $(R_{21})(\mu_{age})$ and $(R_{31})(\mu_{age})$, respectively. This conclusion requires that we temporarily assume that all AD patients are symptomatic. For a person with clinically apparent AD, the distribution of symptom status is the same regardless of age. For patients with AD, the effect of symptom status on mortality is the same regardless of age. This temporary assumption is made in order to be consistent with the presentation of the CERAD data in the literature. This assumption will be dropped later.

Step 3: For patients with AD, estimate the probabilities of transitions to states other than death.

Consider AD patients with mild symptoms. (The calculation method is the same for patients with moderate and severe symptoms). Denote the mortality rate by μ. Denote the CERAD-based overall (i.e., not age-specific) probabilities of transitions from mild to mild, moderate, severe, and death, and p_1, p_2, p_3, and p_4. Among the survivors, define $X_{11}= p_1/(1-p_4)$, $X_{21} = p_2/(1-p_4)$, and X_{31} as $p_3/(1-p_4)$. For any age group, the probability of death is p_4*, and the probability of survival is $1-p_4$* (The distinction between p_4 and p_4* is

that the latter has been estimated separately for each age group, in step 2 above). Obtain the transition probabilities as $X_{11} = (1-p_4^*)$, $X_{21} = (1-p_4^*)$, and $X_{31} = (1-p_4^*)$, respectively. This requires the assumption that for those surviving to the end of the cycle, the RR of transitions to mild, moderate, and severe states is the same regardless of age.

We next turn to estimating the transition probabilities for symptomatic non-AD patients.

Step 4: For symptomatic patients without AD, set all of the above transition probabilities to equal those for patients with AD.

This process is based on the assumption that once a patient becomes symptomatic, in the absence of treatment the course of disease is the same for AD and non-AD patients. (The model will subsequently assume that treatment is only effective for patients with AD).

We next turn to estimating the inputs of the model pertaining to patients without symptoms. These categories, in order of decreasing severity, are MCI, asymptomatic and at increased risk for AD, asymptomatic and not at increased risk for AD.

Step 5: Obtain the annual mortality rate for asymptomatic patients without AD.

This mortality rate was obtained in step 1 above. We assume that this mortality rate applies to each of the subcategories of asymptomatic patients. Asymptomatic patients can only transition to MCI or death. (These transition probabilities will depend on

whether the patient has AD). We are also assuming that the probability of a transition from a symptomatic state of mild, moderate, or severe dementia to a state such as asymptomatic or MCI is impossible. For additional details, please see the discussion of the overall model structure.

Step 6: Obtain the annual mortality rate for asymptomatic patients with AD.
This mortality rate was obtained in step 1 above. An assumption used here is that AD does not have an impact on mortality until symptoms appear.

Step 7: Fill in the probabilities for transitions into the symptomatic states.
Using the literature and expert judgment, we fill in the probabilities of transitions from asymptomatic to MCI for patients without AD, MCI to mild symptoms for patients without AD, asymptomatic to MCI for patients with AD, and MCI to mild symptoms for patients with AD.

For the MCI patients, we assumed that all patients, whether with AD or not, transition to symptoms at the same rate. This rate could thus be estimated from an epidemiological study of the general population of patients with MCI. The percentage of MCI patients having AD was estimated from a combination of the literature and expert judgment.

Efficacy of treatment

Efficacy of treatment is reflected in the decision model by a transition probability multiplier K that influences the probability that a treated patient will move from state i to state j in one year. Specifically,

$$TP^{T}_{i,j} = (K)\ (TP^{NT}_{i,j})$$

where $TP^{NT}_{i,j}$ is the transition probability in the absence of treatment and state j is a more severe state of dementia than i. We assume that treatment does not decrease mortality directly; rather it indirectly decreases mortality by decreasing the likelihood of being in a more severe disability state with a corresponding high mortality rate.
K cannot be estimated from most clinical trials as results are not typically presented in terms of state transitions over time. In the one trial report that presents results as "probability of survival with no clinically evident functional decline" (Mohs, Doody, Morris, et al., 2001), dementia worsening was not isolated from mortality. Since this latter study is otherwise representative of other RCTs, we estimate K from this study alone. We attempt to isolate the effect of treatment on progression to severe dementia by replacing missing mortality data with information from other sources.

Step1: We assume that the survival curves for patients with no clinically evident functional decline will fit to the following declining exponential functions whether or not the patient has been treated:

$$S^{NT}_{t} = \exp(-(\mu_1 + \mu_2 + \mu_3) \times t) \text{ without treatment} \qquad \text{(equation 1)}$$

and

$$S^{T}_{t} = \exp(-((B \times \mu_1) + \mu_2 + \mu_3) \times t) \text{ with treatment,} \qquad \text{(equation 2)}$$

where

μ_1 is the hazard rate of transition from moderate dementia to severe dementia,

μ_2 is the hazard rate of transition from mild dementia to death,

μ_3 is the hazard rate of transition from moderate dementia to death, and

B is a multiplier reflecting the impact of treatment on reducing the rate of transition from moderate dementia to severe dementia.

Step 2: We use equation 1 to estimate μ_1 by replacing S^{NT}_t and t with 0.5 and t' where t' is the time point in the clinical trial when 50% of the initial control population is either dead or have made the transition to severe dementia, replacing the mortality rates (μ_2 and μ_3) with values from a general dementia population of similar mean age to the clinical trial population, and solving algebraically. The validity of this estimate is based on the assumption that mortality in the control group of a trial population is similar to that of a general dementia population of similar mean age.

Step 3: We apply equation 2 to estimate B by using the mortality rates μ_1, μ_2, and μ_3 obtained in the previous step, replacing S^{T}_t and t with 0.5 and t", where t" is the time point in the clinical trial when 50% of the initial treated population is either dead or has made the transition to severe dementia, and then solving algebraically.

Step 4: We convert the rates of transition from moderate to severe dementia [μ_1 for untreated patients and (B) (μ_1) for treated patients] to annual event probabilities by using the rate to probability conversion: $p = 1 - \exp(-((\mu)(t)))$.

Step 5: We divide the probability of transition from moderate to severe dementia with treatment to the same probability without treatment. This ratio is K.

Based on our previous calculations, annual mortality rates for 75-year-old individuals with mild and moderate dementia are .026 and .065, respectively. From the study by Mohs, et al, t" (the time point in the clinical trial when 50% of the initial treated population either died or progressed to severe dementia) is approximately 48 weeks and t' (the time point in the clinical trial when 50% of the initial control population either died or progressed to severe dementia) is approximately 30 weeks. This leads to an estimate for annual rate of transition from moderate dementia to severe dementia of .66 for treated patients ((-ln(.5)/(48/52))-(.026+.065)) and 1.11 for untreated patients ((-ln(.5)/(30/52))-(.026+.065)). The corresponding annual probabilities of progression to severe dementia are .48 and .67. The ratio, K, is 0.72

Table 1: Model assumptions

STRUCTURAL ASSUMPTIONS

1. Model has a one-year cycle i.e., no more than one model event can occur per year.
2. Treatment is based on PET scan; positive results lead to treatment, negative results lead to non-treatment
3. PET has an interpretable result.
4. Every treated individual is affected by the treatment through a reduction in the probability of transition to more symptomatic states as opposed to a fraction of patients being affected by not progressing while the remainder is unaffected.
5. Treatment effects begin at the start of treatment.
6. Treatment effects are constant throughout the duration of treatment.
7. Treatment benefits only those individuals with underlying AD.
8. When treatment stops the effect of treatment stops.
9. Treatment will not be initiated for severe dementia patients; if severe dementia develops during treatment, treatment will be discontinued.

ESTIMATION ASSUMPTIONS

1. PET sensitivity and specificity are estimated from data derived from all sites (i.e., results from academic sites can be extrapolated to community sites and vice versa).
2. Once dementia develops, and after other causes of dementia have ruled out, progression to higher levels of disability occurs at the same rate for untreated AD patients as for non-AD patients, whether treated or not. The assumption is that dementia, no matter what the cause, is inexorably progressive, unless the patient has treated AD.
3. Since Alzheimer's disease is, by definition, a progressive disease, untreated individuals do not transition to less disabled states.
4. Since the benefit of treatment is in stabilizing the existing cognitive state, treated individuals do not transition to less disabled states.
5. Asymptomatic and MCI patients can only progress to the next more severe state in one year. [Note that this is assumption is not made for patients with dementia.]
6. For purposes of calculating age-dependent mortality rates, the relative proportion of MCI, mild, moderate and severe dementia is assumed to be constant. [Note that in the model the distribution of dementia severities will change over time.]
7. The mortality rate of MCI patients is the same as that for the general population.
8. The probability of transition to MCI or to the next state of dementia does not depend on age.

9. The risk ratio of death from an AD vs. a non-AD population is constant over age.
10. For a given level of cognitive function, treatment does not affect mortality rate.
11. For individuals with mild or moderate dementia or with mild cognitive impairment, treatment is continued for 18 months.
12. For asymptomatic individuals at an elevated risk, treatment is continued until a state of severe dementia is reached.
13. The benefits and adverse effects of treatment are constant over age.
14. The only consequence of a treatment adverse event is that treatment is discontinued.
    [Note that this assumption has been made for the current treatment, the structure of the model allows all adverse events.]
15. Utilities for a given level of cognition are unaffected by test results.

Table 2: Description of Markov model states

State	Definition	Allowable Transitions
Asymptomatic – elevated risk	Individual with one other first degree relative (parent, sibling, or child) with AD (Larson, Kukull, and Katzman, 1992)	Asymptomatic-at risk, MCI, mild dementia, moderate dementia, severe dementia, dead
MCI	CDR 0.5	Asymptomatic – at risk*, MCI, mild, moderate, severe, dead
Mild	CDR 1	Asymptomatic – at risk*, MCI*, mild, moderate, severe, dead
Moderate	CDR 2	Asymptomatic – at risk*, MCI*, mild*, moderate, severe, dead
Severe	CDR 3	Asymptomatic – at risk*, MCI*, mild*, moderate*, severe, dead
Dead		Absorbing state

*Transitions that represent an improvement are allowed only for treatment.

Table 3: Input estimates

Input variable description	Baseline value	Range	Comment	Reference
Test operating characteristics				
Sensitivity of PET Scanning	0.86	0.74-0.92		Meta-analysis
Specificity of PET Scanning	0.87	0.78-0.93		Meta-analysis
Utilities				
Utility for asymptomatic state	1	0.50-0.80 of		McMahon et al 2000
Utility for MCI (irrespective of test results)	0.73	base case utilities for all		Neumann et al 2000 Neumann et al 2000
Utility for mild dementia (irrespective of test results)	0.69	states		Neumann et al 2000
Utility for moderate dementia (irrespective of test results)	0.53			
Utility for severe dementia	0.38			
Other estimates used in calculations				
Mortality rates	Age specific	none	Based on life table estimates used for age specific mortality for asymptomatic, MCI and mild dementia patients (see section "Estimation of Inputs")	National Health Statistics
Prevalence of dementia	Age specific	none		Katzman 2001
Prevalence of AD in dementia	0.56	0.50-0.85		Bachman et al 1992 McMahon et al 2000
Prevalence of AD in MCI	0.80	0.70-1.00		Bowen et al 1997 Flicker 1991 Morris et al 1987 Petersen et al 2001 Wolf et al 1998
Lifetime risk of AD in first degree relatives	0.50	0.30-0.70		Lautenschlager et al 1996 Mohs et al 2001
Relative proportions of mild, moderate and severe AD	0.36 mild AD 0.29 moderate AD 0.35 severe AD			Cooper et al 1996

(The estimates stated in the table are those for age 76 years. Calculations have been made for the entire range of ages - from 65 to 99 years.)

Table 4 :Search Strategy

Database: MEDLINE <1966 to July Week 2 2001>

Set	Search	Results
1	exp *alzheimer disease/di, ra	2126
2	exp tomography, emission-computed/	26569
3	and/1-2	143
4	fdg-pet.mp.	1305
5	1 and 4	2
6	or/3,5	143
7	limit 6 to yr=1995-2001	83
8	6 not 7	60
9	pet.tw.	12266
10	fdg-pet.tw.	1305
11	exp alzheimer disease/	24918
12	sensitvity.mp. and specificity/ mp=title,	1
13	exp "sensitivity and specificity"/	105458
14	or/2,4,9-10	30693
15	or/1,11	24918
16	and/14-15	982
17	13 and 16	76
18	6 or 17	202
19	limit 18 to human	199
20	limit 19 to English language	**171**
21	discriminant analysis/	2905
22	21 and 16	13
23	risk factors/	176939
24	23 and 16	29
25	case control studies/	36560
26	25 and 16	47
27	Diagnosis, differential/	216283
28	27 and 16	120
29	or/22,24,26,28	195
30	29 not 18	133
31	limit 30 to human	133
32	limit 31 to English language	**115**

Table 5: Inclusion criteria used for studies included for estimating the operating characteristics of FDG-PET in AD

- Studies were in English language, reported primary data, and were published in a peer review journal (not abstracts).
- Studies included at least 12 human subjects (not animal studies) with the disease of interest.
- For studies of PET operating characteristics,
    - Either clinical diagnosis or histopathological diagnosis was used as the reference standard.
    - Data provided were sufficient to fill in a two-by-two table (PET result versus AD reference standard diagnosis). This criterion implies that patients with and without AD and patients with positive and negative PET results were included in the study.

Table 6: Quality score assigned to studies that were included for estimating the operating characteristics of FDG-PET in AD

- The study had a representative sample of patients with an appropriate spectrum of disease.
- The setting and selection of the population under investigation was clearly described.
- The scanner model or the type and the resolution of the scanner were mentioned.
- Standard criteria were used for test interpretation.
- The test reader and the person assigning reference standard diagnosis were blinded.
- The results were categorized by disease severity.
- The follow-up was complete (no verification bias).
- Histopathological or clinical confirmation was done on the basis of a long-term (>=one year) follow-up with standard criteria.

Table 7: Summary of literature search for the operating characteristics of PET in AD

	No. of articles
Medline preliminary search #1	162
Medline preliminary search #2	113
CINAHL and HealthSTAR searches	7
Cross references	38
Total no. of articles in database	**320**
Abstracts selected for a full-text review by either reviewer	113
Full text articles reviewed by both reviewers till date (includes cross-references)	151
Articles included for data abstraction by both reviewers	**42**
Reasons for exclusion of articles	
(some articles had more than one reason for exclusion)	
Article did not report primary data.	55
Study included less than 12 human subjects	12
Study did not use PET-FDG	36
The diagnostic criteria used were not related to disease status (severity)	3
Data was not adequate to fill in a two-by-two table	45
Articles finally included in the evidence tables	**18**

Results

In the following sections, we detail the results of the analysis of PET for patients who may have AD. The presentation is organized by three scenarios defined by patient presentation: Scenario A – mild to moderate dementia; Scenario B – mild cognitive impairment; and Scenario C – asymptomatic but with a first-degree relative with AD.

Scenario A: Mild to moderate dementia

What are the possible clinical management options and outcomes for this scenario?

Individuals who present with documented dementia and who do not have evidence of a non-AD etiology of their condition are candidates for treatment with AChE-I medications (Knopman, DeKosky, Cummings, et al., 2001) as well as other supportive interventions for patient, family/caregivers (Marriott, Donaldson, Tarrier, et al., 2000; Mittelman, Ferris, Shulman, et al., 1996). Because treatment has been demonstrated in clinical trials to be effective and is relatively well tolerated by most patients with AD dementia, AChE-I treatment for all patients with mild to moderate dementia is common practice (See below: "What are the benefits and adverse effects of AChE-I therapy when used for patients in the scenario?"). This strategy of treating all patients with a diagnosis of AD after a standard work-up is denoted in this section as "Treat All". A second possible strategy is to test with PET and to treat only those individuals with results consistent with AD (denoted "Test"). The third possible strategy to consider is to not test or treat (denoted "No Test/No Treat").

Categories of outcomes include physical outcomes, psychological outcomes, legal outcomes, and ethical outcomes. Costs are not considered explicitly. Physical outcomes include life expectancy, quality-adjusted life expectancy, and severe dementia-free life expectancy. In the decision model the psychological, legal, and ethical domains are represented by the surrogate measures – proportion of patients falling into the 4 categories: (1) true positive (with AD and treated), (2) false positive (without AD and treated), (3) true negative (without AD and not treated) and (4) false negative (with AD and not treated). We also considered correct diagnoses (true positives plus true negatives).

Note that when considering the impact of treatment, we consider only AChE-I therapy, as the appropriateness of all other treatments such as vitamin E, medications for symptom relief, and psychosocial interventions does not depend on the specific diagnosis of AD.

What is the diagnostic performance of PET in this scenario?

Ideally, we should base our estimates of the diagnostic performance of FDG-PET on studies that test its ability to distinguish AD from other causes of dementia among representative samples of patients presenting with dementia. However, available data in the literature far more frequently describes the ability of FDG-PET to distinguish AD from normal control subjects. Such studies can be expected to overestimate the diagnostic performance of FDG-PET.

We describe first the few studies that describe discrimination between AD and non-AD dementia and second the majority of studies which describe discrimination of AD from normal control subjects.

Three studies describe the ability of FDG-PET to discriminate patients with AD from those with other causes of dementia (Salmon 1994; Hoffman 2000; Silverman 2001).

Salmon et al.(Salmon, Sadzot, Maquet, et al., 1994) included patients with mild, moderate and severe dementia. Sixteen of 65 AD patients had mild dementia and 25 AD patients had moderate dementia. For 64 non-AD dementia control patients, the severity of dementia was not described. While AD diagnoses were based on NINCDS-ADRA criteria, the basis for non-AD dementia diagnoses was not described. In the overall study population, which included patients with severe dementia, operating characteristics of FDG-PET for distinguishing AD from vascular dementia included sensitivity of 86% and specificity of 61%. This study described results stratified by severity of dementia only for patients with AD, permitting calculation of sensitivity for three subsets of patients: sensitivity of FDG-PET was 75% for patients with mild AD, 88% for patients with moderate AD, and 92% for patients with severe AD. While a trend in the point estimates appears to be present, the number of subjects is too small for these differences to be statistically significant.

Hoffman et al did not describe the severity of dementia in the study population. They used histopathology as their reference standard. This reference standard is more

definitive than the standard clinical evaluation used by most other studies. The resulting analysis give sensitivity of 88% and specificity of 67%, results very close to the figures for Salmon, Sadzot, Maquet, et al.,1994.

Silverman et al recently reported a large study of FDG-PET for diagnosis of AD versus other causes of dementia (Silverman, Small, Chang, et al., 2001). This study reports on two populations, a prospective cohort of patients that received long-term clinical follow-up and a retrospective cohort of patients with a histopathological reference standard. In addition, the study reported an association between PET results and progression of disease, an outcome not assessed by previous studies. Among patients with a histopathological diagnosis, the sensitivity of FDG-PET for diagnosing AD was 94% (91/97; 95% CI, 89% to 99%) and the specificity was 73% (30/41; 95% CI, 60% to 87%). In the subset of patients with questionable or mild dementia at the time of PET, the diagnostic performance was similar: sensitivity 95% (89% to 100%) and specificity 71% (48% to 95%).

These three studies provide estimates for the sensitivity and specificity of FDG-PET in distinguishing AD from non-AD dementia. They are few in number and somewhat variable, with sensitivity ranging from 86% to 95% and specificity ranging from 61% to 74%.

In addition to these three studies there were five studies that describe the operating characteristics of PET in discriminating between patients with dementia due to AD and

specific etiologies of non-AD dementias: multi-infarct dementia (Duara, Barker, Lowenstein et al., 1989), vascular dementia (Mielke, Pietrzyk, Jacobs, et al., 1994; Szelies, Mielke, et al., 1994) and dementia with Lewy bodies (Ishii, Imamura, Yamaji, et al., 1998; Higuchi, Tashiro, Arai, et al., 2000). In these studies the sensitivity of PET ranged from 88%- 90% and the specificity ranged from 18%-86%.

To further investigate the variability of PET diagnostic data and to provide additional data for the model estimates, we also analyzed studies that describe discrimination between patients with AD and normal controls.

Fifteen studies compared patients with AD at different stages of dementia to normal controls (Azari, Pettigrew, Schapiro, et al., 1993; Burdette, Minoshima, Vander Borght, et al., 1996; Duara, Barker, Loewenstein, et al., 1989; Fazekas, Alavi, Chawluk, et al., 1989; Grady, Haxby, Schapiro, et al., 1990; Herholz, 1990; Herholz, Perani, Salmon, et al., 1993; Higuchi, Tashiro, Arai, et al., 2000; Ishii, Imamura, Sasaki, et al., 1998; Kippenhan, Barker, Pascal, et al., 1992; Messa, Perani, Lucignani, et al., 1994; Mielke, Pietrzyk, Jacobs, et al., 1994; Minoshima, Frey, Foster, et al., 1995; Ohyama, Senda, Mishina, et al., 2000; Szelies, Mielke, Herholz, et al., 1994).

Table 8 summarizes the characteristics of the principal study subjects and the operating characteristics for PET from these studies.

Five studies did not explicitly report sensitivity and specificity values. Four of these studies provided plots of metabolic ratio for patients with AD and controls (Herholz,

Perani, Salmon, et al., 1993; Higuchi, Tashiro, Arai, et al., 2000; Ishii, Imamura, Sasaki, et al., 1998; Mielke, Pietrzyk, Jacobs, et al., 1994). A fifth study presented the ROC curves for the test (Kippenhan, Barker, Pascal, et al., 1992). For these studies we decided to use a cut-off point value of 90% for the specificity, which allowed us to estimate the specificity from the plots or ROC curves. Specificity estimates in these five studies ranged from 17% to 85%.

For the other ten studies that provided sensitivity and specificity estimates, sensitivity ranged from 61% to 100%, and specificity from 54% to 100.

A meta-analysis was performed with "Meta-Test" version 0.6. For this analysis, the five studies that did not explicitly report sensitivity and specificity were excluded. The remaining studies demonstrated heterogenous estimates of sensitivity and specificity. For these remaining studies, a random effects model was used (Figure 2) producing a pooled sensitivity estimate (95% CI) for distinguishing normal healthy controls from patients with AD of 88% (79% to 94%), and a pooled specificity estimate of 87% (77% to 93%).

What are the benefits and adverse effects of AChE-I therapy when used for patients in this scenario?

As described in the "Introduction", practice guidelines recommend treating AD patients with currently available and approved AChE-I medications: donepezil (Aricept), rivastigmine (Exelon) or galantamine (Reminyl)(Doody, Stevens, Beck, et al., 2001). In

multiple RCTs, AChE-I agents have been shown to delay the onset of progression by approximately 6 months. [RCT evidence] (Doody, Stevens, Beck, et al., 2001). Approximately 10-20% of patients are unable to tolerate therapy due to minor, transient side effects primarily leading to drug discontinuation (Burns, Rossor, Hecker, et al., 1999; Birks and Flicker 2001). As detailed in "*Methods*", the approach we took to converting trial results to an estimate of treatment effect on probability of progression of disease translates to a relative risk of progression of 0.72.

For a patient with dementia which strategy is most likely to provide better health outcomes?

For scenario A the decision model was applied separately to a moderate dementia cohort and a mild dementia cohort. Since results for both cohorts were substantively similar and the results for mild dementia patients were more favorable to PET scanning (Table 9a), we limit our presentation here to patients with mild dementia.

Base-case analysis: In the base case, "Treat All" is preferred over either "Test" or "No Test/No Treat", in terms of quality-adjusted life expectancy (Table 9a), life expectancy, or severe-dementia-free life expectancy. The "Test" strategy is preferred only by the measure "percentage correct diagnosis" (proportion of patients who are true positive or true negative).

One-way sensitivity analyses*:* The relative preference for the three strategies is unaffected by changing the following input values over their plausible range: PET

sensitivity or specificity, prevalence of AD, effectiveness of treatment, duration of treatment effectiveness, percentage of complications or discount rate. However, when treatment complications are equivalent to mortality, treating all patients becomes the least preferred strategy.

Hypothetical treatments with onerous complications: Sensitivity analysis suggests that while the "Treat All" strategy is optimal when treatment is relatively benign and at least modestly effective, the strategy becomes less attractive when treatment complications loom large enough to become more equivalent to mortality. To further explore the impact of treatment complications on preferred strategy, we considered several hypothetical treatments characterized by a variety of negative characteristics. These include a treatment with long-term effects manifest as either a decrease in utility (50% reduction in utility for 1 year or 20% reduction in utility for a lifetime), an increase in rate of progression of disease (relative risk for progression of 2 for 1 year), or an increase in the mortality rate (relative risk for death of 5 for 1 year).

All hypothetical treatments considered within this sensitivity analysis lead to "Test" being preferred in terms of either quality-adjusted life expectancy or severe dementia-free life expectancy (Table 9a). Since one would not choose a therapy that was as efficacious as AChE-I but had worse complications, we performed a two-way analysis to examine the interaction between treatment efficacy (in terms of relative risk of progression) and change in quality of life with treatment (in terms of utility change relative to the utility for mild dementia). We did this by varying widely the values of these two inputs, and by

plotting the territories on the efficacy/ complication utility plane in which one strategy is preferred over others. These results are shown in Figure 3. As noted in one-way sensitivity analysis, this figure reveals that “Test” becomes more attractive as utility with complications becomes worse (one moves down the plane). However, if efficacy is simultaneously increased (one moves towards the left on the plane) “Test” becomes less attractive. This observation indicates that the optimal strategy in the face of a treatment with more onerous complications cannot be predicted without also knowing the concomitant improvement in effectiveness. It should be noted here that the relative benefit of “Test” is at a maximum of 0.03 QALYs (11 days) when the hypothetical treatment has a complication with a utility equivalent to death.

Scenario B: Mild cognitive impairment

What are the possible clinical management options and outcomes for this scenario?

Individuals presenting with mild cognitive impairment but without the functional impairment required for the diagnosis of dementia are often treated with AChE-I. However the evidence for this practice is lacking (as noted below in “What are the benefits and adverse effects of AChE-I therapy when used for patients in the scenario?”). If the evidence for AChE-I medication effectiveness can be extrapolated to the MCI population, the rationale for AChE-I treatment is that delaying the onset of dementia is even more valuable than delaying the onset of severe dementia for those already experiencing mild to moderate functional impairment and that MCI patients are

very likely to progress to dementia. Indeed, it appears that the proportion of MCI patients with AD is greater than the proportion of demented patients with AD (Mohs, Breitner, Silverman, et al., 1987; Morris, McKeel, Storandt, et al., 1991). As with Scenario A, three major management strategies are possible for individuals with MCI. The first is to treat based on clinical findings ("Treat All"). The second is to test with PET and to treat only those individuals with PET results consistent with AD ("Test"). The third is to not treat ("No Test/No Treat").

Clinical outcomes considered include life expectancy, quality-adjusted life expectancy, dementia-free life expectancy, and proportion of patients falling into the 4 categories, true positive (with AD and treated), false positive (without AD and treated), true negative (without AD and not treated) and false negative (with AD and not treated). We also considered proportion of patents with true diagnoses (true positive plus true negative).

What is the diagnostic performance of PET in this scenario?

Only two studies provided sub-group analysis by degree of dementia. Burdette et al. divided their population of patients with AD into two groups (Burdette, Minoshima, Vander Borght, et al., 1996). In the group of 28 patients with questionable or mild dementia the sensitivity of PET was 79%. The sensitivity was 100% in the group of 11 patients with moderate to severe dementia (MMSE < 15). In another study, Fazekas et al. reported a sensitivity of 100% for patients with mild to moderate dementia (MMSE > 15) and of 93% for patients with moderate to severe dementia (MMSE < 15) (Fazekas, Alavi, Chawluk, et al., 1989).

These data, along with the data on difference in performance by dementia severity described previously, suggest that diagnostic performance of FDG-PET may be less accurate for less severe forms of AD. However, because there is no data among subjects with MCI, we use the conservative assumption that diagnostic performance is the same as that in mild-moderate dementia.

What are the benefits and adverse effects of AChE-I therapy when used for patients in this scenario?

No trials were identified for the use of AChE-I drugs or other treatments in MCI patients.

For a patient with mild cognitive impairment, which strategy is most likely to provide better health outcomes?

Table 9b presents the results for the base case and sensitivity analysis for patients with MCI. The results are substantively the same as for Scenario A. Again, the "Treat All" strategy is preferred in the base case, except by the measure of "proportion correct diagnosis". The base case results are robust by sensitivity analysis, although hypothetical treatments with especially bad consequences would cause "Test" to become preferred. Also, as with Scenario A, the two-way analysis examining the impact of changes in treatment efficacy concurrent with a decline in utility for patients with complications reveals that a treatment that has both greater efficacy and more onerous complications can lead to "Test" being less preferred (Figure 4).

Scenario C: Asymptomatic with a first-degree relative with AD

What are the possible clinical management options and outcomes for this scenario?

Unlike Scenarios A and B, treatment with AChE-I medications is neither recommended nor common. Like Scenario B, there is no evidence that individuals at an elevated risk will benefit from such treatment by a delayed progression of disease (see below: "What are the benefits and adverse effects of AChE-I therapy when used for patients in the scenario?"). However, the current hypothesis is t is hypothesized that for patients who are destined to manifest AD, treatment can delay the progression. Thus, we evaluated the same management strategies for asymptomatic, high-risk individuals as for symptomatic individuals: treat preemptively ("Treat All"), test with PET, and treat only those individuals with results consistent with AD ("Test"), and neither test nor treat ("No Test/No Treat").

Categories of outcomes include physical outcomes, psychological outcomes, legal outcomes, and ethical outcomes. Costs were not considered explicitly. Physical outcomes include life expectancy, quality-adjusted life expectancy, and dementia-free life expectancy. In the decision model the psychological, legal, and ethical domains were represented by the surrogate measures: proportion of patients falling into the four categories, true positive (with AD and treated), false positive (without AD and treated),

true negative (without AD and not treated) and false negative (with AD and not treated). We also considered correct diagnoses (true positives plus true negatives).

What is the diagnostic performance of PET in this scenario?

No studies exploring the use of PET in asymptomatic at risk patients satisfied our inclusion criteria for abstraction.

What are the benefits and adverse effects of AChE-I therapy when used for patients in this scenario?

No trials were identified for the use of AChE-I drugs or other treatments in asymptomatic individuals at an elevated risk for AD.

For an asymptomatic patient with a family history of AD, which strategy is most likely to provide better health outcomes?

***Base-case analysis*:** For asymptomatic high-risk individuals, the "Treat All" strategy is preferred in terms of life expectancy, quality-adjusted life expectancy, and dementia-free life expectancy (Table 9c). The "Test" strategy is second, except for the proportion of patients with correct diagnosis; as with the symptomatic scenarios, the "Test" strategy leads to the highest proportion of true positives plus true negatives.

***Sensitivity analyses*:** As with the symptomatic scenarios, the preference for "Treat All" is robust for all variations of the following inputs over their plausible ranges: PET sensitivity or specificity, prevalence of AD, efficacy of treatment, duration of treatment,

probability of treatment complications or discount rate. In all one-way sensitivity analyses, “Test” is consistently the second preferred strategy. When complications are treated like an event (death or progression), the “No Treat” strategy is preferred.

Hypothetical treatments with onerous complications: The effect of hypothetical treatments with especially onerous complications was not as consistent as with the symptomatic scenarios (Table 9c). For patients in Scenario C testing would be preferred only for complications that reduce utility by 50% for 1 year, or by 20% for a lifetime. The “Treat All” strategy is the preferred strategy if complications are modeled as leading either to increased risk of progression to dementia or to an increased risk of death. As with the two-way sensitivity analysis results for scenarios A and B, a severe short-term disutility tends to make “Test” more attractive, but this effect is strongly modulated by the effectiveness of the new treatment. As effectiveness improves, “Test” may become less preferred (Figure 5). It is notable that the territory of the treatment efficacy/complication utility plane appears wider for scenario C as compared to scenarios A and B. This is in part because the rate of progression in asymptomatic patients is quite slow so that true positive (more likely in the “Treat” strategy) becomes less important and true negative (more likely in the “Treat” strategy) becomes relatively more important. To clarify this, we performed a sequence of 3 one-way sensitivity analyses, each analysis for a different level of treatment efficacy (Figure 5b, 5c, and 5d, correspond to a relative risk for progression with treatment of 0.8, 0.5, and 0.3, respectively). The maximum relative benefit of “Test” is 0.037 QALYs (14 days) when the hypothetical treatment has an efficacy of approximately 0.8 (a treatment not as

efficacious as that for an AChE-I) and a complication utility value of approximately 0.35 As seen in Figures 5cand 5d, the relative benefit of testing attains a maximum value for QALYs only when a treatment is effective enough to decrease the rate of disease progression by a factor of 0.5. It attains a maximum value of 15 days when the treatment decreases the rate of progression by a factor of 0.3 and when complications are equivalent to mortality.

What are the legal, ethical and psychosocial impacts of receiving a dementia diagnosis for individuals best represented by one of the three scenarios?

In patients with mild to moderate dementia the decision analysis provides an assessment of the impact of PET in terms of improvement in cognition and freedom from treatment complications. Issues not directly addressed include the legal, ethical, and psychosocial impact of receiving a diagnosis of AD, whether correct or incorrect, or of failing to be treated as AD.

The entire concept of an ethical, psychosocial or legal impact of testing or not testing is based on the state of the disease that the patient is in at the current time and the possibility of the progression of the disease. There have been studies that deal with various aspects of testing and its impact on individuals and their families – the aspects of autonomy, maleficence, the three forms of beneficence, justice (especially distributive justice), liability and the effects on employability and insurance. The impacts of testing appear to affect individuals in Scenarios B and C (mild cognitive impairment and

asymptomatic high-risk), more than those in Scenario A (mild and moderate dementia). Table 10 illustrates some of the salient points.

Table 8: Studies exploring the operating characteristics of PET for differentiating patients with AD from normal controls.

Study	AD population	Controls	PET characteristics	Operating Characteristics TP	FN	FP	TN	Sens	Spec	Quality Score	No. in S-ROC curve
Azari et al. 1993, data collection dates NR Bethesada (NIH), Maryland	19, 10 with mild dementia, 19 with moderate dementia Age (range): 52-81	22 healthy controls Age (range): 53-75	*Scanner*: Scanditronix PC1024-7B *Criteria for positivity*: fronto-parietal hypometabolism	18	1	1	20	95%	95%	1	6
Burdette et al. 1996, data collection 1989-92 Ann Arbor, Michigan	39, 28 with MCI or mild dementia, 11 with moderate/severe dementia Mean ± SD age: 68 ± 7.6	22 healthy controls Mean ± SD age: 64 ± 7.5	*Scanner*: 931/08-12 CTI *Criteria for positivity*: symmetrical parieto-temporal hypometabolism	33	6	5	35	85%	88%	5	1
Duara et al. 1989, data collection dates NR Miami Beach, Florida	50 Mean ± SD age: 72.8 ± 9.7	20 young healthy controls, Mean ± SD age: 41.5 ± 9.9 41 older healthy controls, Mean ± SD age: 67.2 ± 8.9	*Scanner*: PETT V *Criteria for positivity:* hypometabolism index	44 44	6 6	10 19	19 22	88% 88%	66% 54%	5	2
Fazekas et al. 1989, data collection dates NR Philadelphia, Pennsylvania	30, 14 with mild/moderate dementia, 16 with moderate/severe dementia Mean age: 65	25 age-matched controls Mean age: 65	*Scanner*: PETT V *Criteria for positivity*: any hypometabolism	27	1	4	21	96%	84%	5	5
Grady et al. 1990, data collection dates NR Bethesda, Maryland	33 Mean ± SD age: 68.5 ± 9.5	41 healthy controls Mean ± SD age: 64.9 ± 10.9	*Scanner*: Scanditronix PC1024-7B *Criteria for positivity*: parieto-temporal hypometabolism, controls all considered as negative	20	13	0	41	61%	100%	3	3
Herholz et al. 1990, data collection dates NR Köln, Germany	19 Mean ± SD age: 60.6 ± 7.1	19 healthy controls Mean ± SD age: 61.1 ± 10.2	*Scanner*: Scanditronix PC-384 *Criteria for positivity*: any hypometabolism	19	0	0	19	100%	100%	2	8

Study	AD population	Controls	PET characteristics	Operating Characteristics TP FN FP TN Sens Spec	Quality Score	No. in S-ROC curve
Herholz et al. 1993, data collection dates NR Germany, Italy, Belgium	37 Mean ± SD age: 65.2 ± 7.4	34 healthy controls Mean ± SD age: Italy 44.6 ± 15.7, Belgium 58.2 ± 8.0, Germany 65.4 ± 7.3	*Scanner*: Italy Ecat 931/04-12, Belgium NeuroEcat, Germany Scanditronix PC-384 *Criteria for positivity*: not reported. A cut-off point at which sensitivity is 90% was chosen by the reviewers	33 4 5 28 89% 85%	1	X
Higuchi et al. 2000, data collection dates NR Sendai, Japan	11 Mean ± SD age: 66.5 ± 5.7	10 normal controls Mean ± SD age: 65.0 ± 8	*Scanner:* SET2400W, Shimadzu *Criteria for positivity*: metabolic ratio. A cut-off point at which sensitivity is 90% was chosen by the reviewers	10 1 7 3 91% 30%	2	X
Ishii et al. 1998, data collection dates NR Himeji, Japan	12 Mean ± SD age: 73.2 ± 6.3	12 normal controls Mean ± SD age: 72.8 ± 4.9	*Scanner*: Headtome IV, Shimadzu *Criteria for positivity*: any hypometabolism. A cut-off point at which sensitivity is 90% was chosen by the reviewers	11 1 10 2 92% 17%	3	X
Kippenham et al. 1992, data collection dates NR Miami, Florida	41 Mean ± SD age: 70.9 ± 8.8	50 normal controls Mean ± SD age: 67.7 ± 8.9	*Scanner*: PETT V *Criteria for positivity*: any deficit present. A cut-off point at which sensitivity is 90% was chosen by the reviewers	37 4 15 35 90% 70%	2	X

Study	AD population	Controls	PET characteristics	Operating Characteristics TP FN FP TN Sens Spec	Quality Score	S-ROC curve
Messa et al. 1994, data collection dates NR Milan, Italy	21 Mean ± SD age: 62.8 ± 7.8	10 normal controls Mean ± SD age: 47 ± 13	*Scanner*: 931/04-12 CPS/Siemens *Criteria for positivity*: out of mean ± 2 SD	21 0 1 9 100% 90%	1	10
Mielke et al. 1994, data collection dates NR Köln, Germany	10 Mean ± SD age: 68.8 ± 5.6	13 normal controls Mean ± SD age: 59.5 ± 11.1	*Scanner*: ECAT, Siemens *Criteria for positivity*: metabolic ratio. A cut-off point at which sensitivity is 90% was chosen by the reviewers	18 2 5 8 90% 62%	2	X
Minoshima et al. 1995, data collection 1989-92 Ann Arbor, Michigan	37 Mean ± SD age: 64 ± 8	22 normal controls Mean ± SD age: 68 ± 7	*Scanner*: ECAT, Siemens *Criteria for positivity*: glucose metabolic rate in parieto-temporal cortex	36 1 0 22 97% 100%	4	4
Ohyama et al. 2000, data collection dates NR Tokyo, Japan	21 Mean ± SD age: 61 ± 10	10 normal controls Mean ± SD age: 55 ± 12	*Scanner*: Headtome IV *Criteria for positivity*: any hypometabolism	18 3 1 9 86% 90%	5	9
Szelies et al. 1994, data collection dates NR Köln, Germany	24, 14 patients with mild dementia, 10 patients with moderate dementia Mean ± SD age: 65.9 ± 7.6	15 normal controls Mean ± SD age: 60 ± 7.3	*Scanner:* Scanditronix 384 *Criteria for positivity*: metabolic ratio	18 6 5 10 75% 67%	2	7

TP = True Positive, FN = False Negative, FP = False Positve, TN = True Negative

Table 9a: Results- Mild dementia

(QALY=Quality of life, LE=Life expectancy, SDFLE=Severe dementia free life expectancy)

OUTCOMES								
	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Base Case								
Treat all	4.099	7.890	4.015	0.560	0.440	0.000	0.000	56%
Test	4.0902	7.881	3.996	0.490	0.060	0.070	0.380	87%
No test/No treat	4.024	7.818	3.862	0.000	0.000	0.560	0.440	44%
Sensitivity Analyses								
PET sensitivity low = 0.79								
Treat all	4.099		4.015					
Test	4.083		3.983					
No test/No treat	4.024		3.862					
PET sensitivity high = 0.94								
Treat all	4.099		4.015					
Test	4.095		4.006					
No test/No treat	4.024		3.862					
PET specificity low = 0.73								
Treat all	4.099		4.015					
Test	4.090		3.996					
No test/No treat	4.024		3.862					
PET specificity high = 0.93								
Treat all	4.099		4.015					
Test	4.090		3.996					
No test/No treat	4.024		3.862					
Prevalence AD low = 50%								
Treat all	4.091		3.998					
Test	4.083		3.982					
No test/No treat	4.024		3.8618					
Prevalence AD high = 85%								
Treat all	4.138		4.094					
Test	4.125		4.066					
No test/No treat	4.024		3.862					

SENSITIVITY ANALYSES (cont.)

	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Prevalence AD=0%								
Treat all	4.024		3.862					
Test	4.024		3.862					
No test/No treat	4.024		3.862					
Prevalence AD=100%								
Treat all	4.159		4.135					
Test	4.143		4.102					
No test/No treat	4.024		3.862					
RR progression=0								
Treat all	4.396		4.585					
Test	4.352		4.499					
No test/No treat	4.024		3.862					
RR progression = 0.5								
Treat all	4.160		4.135					
Test	4.144		4.102					
No test/No treat	4.024		3.862					
RR progression = 1								
Treat all	4.024		3.862					
Test	4.024		3.862					
No test/No treat	4.024		3.862					
Length of efficacy = 12 months								
Treat all	4.077		3.966					
Test	4.071		3.953					
No test/No treat	4.024		3.862					
Length of efficacy = lifetime								
Treat all	4.276		4.445					
Test	4.246		4.375					
No test/No treat	4.024		3.862					

SENSITIVITY ANALYSES (cont.)

	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Treatment complications = 0%								
Treat all	4.113		4.042					
Test	4.102		4.021					
No test/No treat	4.024		3.862					
Treatment complications = 30%								
Treat all	4.086		3.988					
Test	4.078		3.973					
No test/No treat	4.024		3.862					
Treatment complications =100%								
Treat all	4.024		3.862					
Test	4.024		3.862					
No test/No treat	4.024		3.862					
Discount rate = 0%								
Treat all	4.709		4.384					
Test	4.698		4.363					
No test/No treat	4.619		4.208					
Discount rate 5%								
Treat all	3.773		3.803					
Test	3.765		3.786					
No test/No treat	3.705		3.663					
Complications = death								
Treat all		6.791	3.510					
Test		7.277	3.719					
No test/No treat		7.812	3.862					

HYPOTHETICAL SCENARIOS								
	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
50% short-term decrease in utility								
Treat all	4.055							
Test	4.066							
No test/No treat	4.024							
20% lifetime decrease in utility								
Treat all	3.994							
Test	4.032							
No test/No treat	4.024							
RR for progression = 2								
Treat all	4.039		3.898					
Test	4.057		3.932					
No test/No treat	4.024		3.862					
RR for death = 5								
Treat all	4.060		3.973					
Test	4.068		3.973					
No test/No treat	4.024		3.862					

Table 9b: Results- MCI

(QALY=Quality of life, LE=Life expectancy, DFLE=Dementia free life expectancy)

OUTCOMES								
	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Base Case								
Treat all	6.660	10.225	5.614	0.800	0.200	0.000	0.000	80%
Test	6.650	10.216	5.592	0.700	0.030	0.100	0.170	87%
No test/No treat	6.577	10.149	5.431	0.000	0.000	0.800	0.200	20%
Sensitivity Analyses								
PET sensitivity low = 0.79								
Treat all	6.660		5.614					
Test	6.643		5.576					
No test/No treat	6.577		5.431					
PET sensitivity high = 0.94								
Treat all	6.660		5.614					
Test	6.655		5.603					
No test/No treat	6.577		5.431					
PET specificity low = 0.73								
Treat all	6.660		5.614					
Test	6.650		5.592					
No test/No treat	6.577		5.431					
PET specificity high = 0.93								
Treat all	6.660		5.614					
Test	6.650		5.592					
No test/No treat	6.577		5.431					
Prevalence AD low = 0%								
Treat all	6.577		5.431					
Test	6.577		5.431					
No test/No treat	6.577		5.431					
Prevalence AD low = 70%								
Treat all	6.645		5.591					
Test	6.641		5.572					
No test/No treat	6.577		5.431					

SENSITIVITY ANALYSES (cont.)								
	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Prevalence AD high = 100%								
Treat all	6.681		5.660					
Test	6.668		5.632					
No test/No treat	6.577		5.431					
RR progression = 0(treatment is 100% effective)								
Treat all	6.965		6.319					
Test	6.918		6.213					
No test/No treat	6.577		5.431					
RR progression = 0.5								
Treat all	6.725		5.761					
Test	6.707		5.721					
No test/No treat	6.577		5.431					
RR progression = 1								
Treat all	6.577		5.431					
Test	6.577		5.431					
No test/No treat	6.577		5.431					
Length of efficacy = 12 months								
Treat all	6.633		5.559					
Test	6.626		5.544					
No test/No treat	6.577		5.431					
Length of efficacy = lifetime								
Treat all	7.120		6.265					
Test	7.041		6.149					
No test/No treat	6.577		5.431					

SENSITIVITY ANALYSES (cont.)								
	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Treatment complications = 0%								
Treat all	6.675		5.646					
Test	6.663		5.621					
No test/No treat	6.577		5.431					
Treatment complications = 30%								
Treat all	6.646		5.582					
Test	6.637		5.564					
No test/No treat	6.577		5.431					
Treatment complications = 100%								
Treat all	6.577		5.431					
Test	6.577		5.431					
No test/No treat	6.577		5.431					
Discount rate = 0%								
Treat all	8.116		6.578					
Test	8.103		6.552					
No test/No treat	8.003		6.359					
Discount rate 5%								
Treat all	5.930		5.117					
Test	5.922		5.097					
No test/No treat	5.861		4.952					
Complications = death								
Treat all		9.485	4.874					
Test		9.676	5.052					
No test/No treat		10.149	5.431					

HYPOTHETICAL SCENARIOS								
	QALY	LE	SDFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
50% short-term decrease in utility								
Treat all	6.608							
Test	6.612							
No test/No treat	6.577							
20% lifetime decrease in utility								
Treat all	6.478							
Test	6.517							
No test/No treat	6.577							
RR for progression = 2								
Treat all	6.620		5.513					
Test	6.618		5.518					
No test/No treat	6.577		5.431					
RR for death = 5								
Treat all	6.596		5.557					
Test	6.603		5.551					
No test/No treat	6.577		5.431					

Table 9c: Results- Asymptomatic elevated risk

(QALY=Quality of life, LE=Life expectancy, DFLE=Dementia free life expectancy)

OUTCOMES								
	QALY	LE	DFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Base Case								
Treat all	12.248	12.786	12.206	0.500	0.500	0.000	0.000	50%
Test	12.231	12.776	12.185	0.440	0.600	0.060	0.440	88%
No test/No treat	12.106	12.707	12.032	0.000	0.000	0.500	0.500	50%
Sensitivity Analyses								
PET sensitivity low = 0.79								
Treat all	12.248		12.206					
Test	12.218		12.170					
No test/No treat	12.106		12.032					
PET sensitivity high = 0.94								
Treat all	12.248		12.206					
Test	12.240		12.196					
No test/No treat	12.106		12.032					
PET specificity low = 0.73								
Treat all	12.248		12.206					
Test	12.231		12.185					
No test/No treat	12.106		12.032					
PET specificity high = 0.93								
Treat all	12.248		12.206					
Test	12.231		12.185					
No test/No treat	12.106		12.032					
Prevalence AD low = 0%								
Treat all	12.106		12.032					
Test	12.106		12.032					
No test/No treat	12.106		12.032					
Prevalence AD low = 30%								
Treat all	12.191		12.136					
Test	12.181		12.124					
No test/No treat	12.106		12.032					

SENSITIVITY ANALYSES (cont.)								
	QALY	LE	DFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Prevalence AD high = 70%								
Treat all	12.305		12.276					
Test	12.277		12.242					
No test/No treat	12.106		12.032					
Prevalence AD high = 100%								
Treat all	12.390		12.380					
Test	12.356		12.338					
No test/No treat	12.106		12.032					
RR progression = 0								
Treat all	12.521		12.479					
Test	12.471		12.425					
No test/No treat	12.106		12.032					
RR progression = 0.5								
Treat all	12.349		12.328					
Test	12.320		12.292					
No test/No treat	12.106		12.032					
RR progression = 1								
Treat all	12.106		12.032					
Test	12.106		12.032					
No test/No treat	12.106		12.032					
Length of efficacy = 12 months								
Treat all	12.119		12.046					
Test	12.117		12.045					
No test/No treat	12.106		12.032					
Length of efficacy = lifetime (base case)								
Treat all	12.248		12.206					
Test	12.231		12.182					
No test/No treat	12.106		12.032					

SENSITIVITY ANALYSES (cont.)								
	QALY	LE	DFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
Treatment complications = 0%								
Treat all	12.273		12.236					
Test	12.253		12.212					
No test/No treat	12.106		12.032					
Treatment complications = 30%								
Treat all	12.223		12.175					
Test	12.209		12.158					
No test/No treat	12.106		12.032					
Discount rate = 0%								
Treat all	16.302		16.206					
Test	16.273		16.172					
No test/No treat	16.064		15.919					
Discount rate 5%								
Treat all	10.401		10.380					
Test	10.389		10.365					
No test/No treat	10.297		10.252					
Complications = death								
Treat all		11.056	10.476					
Test		11.903	11.312					
No test/No treat		12.707	12.032					

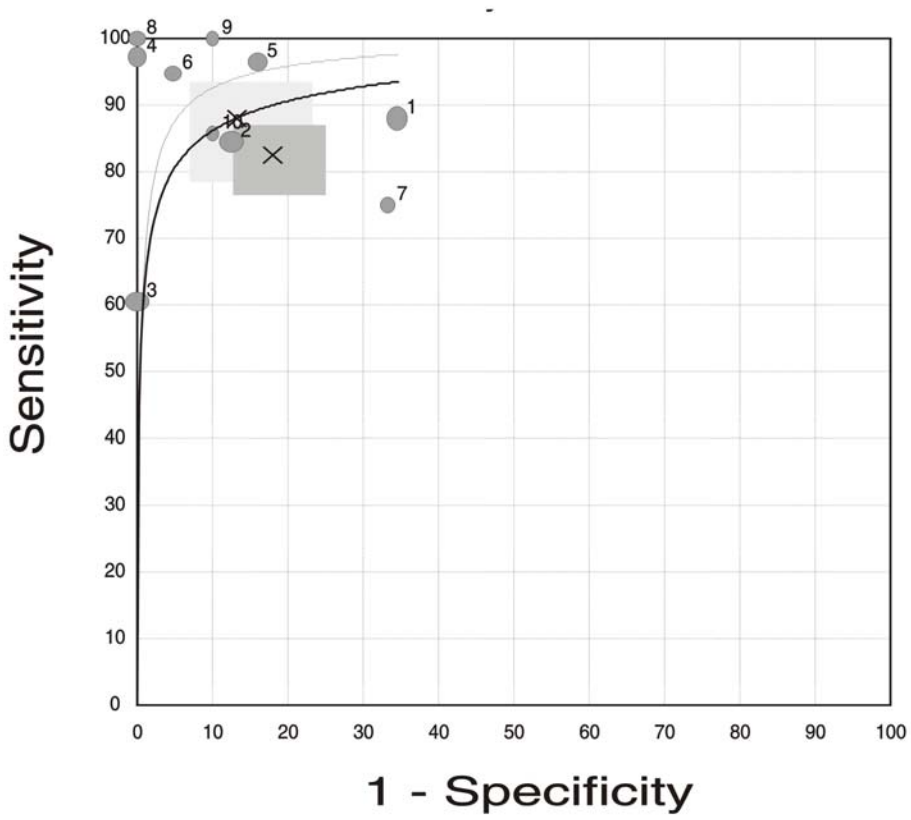
HYPOTHETICAL SCENARIOS								
	QALY	LE	DFLE	True Positives	False Positives	False Negatives	True Negatives	Percentage correct diagnosis
50% short-term decrease in utility								
Treat all	12.177							
Test	12.195							
No test/No treat	12.106							
20% lifetime decrease in utility								
Treat all	11.900							
Test	12.055							
No test/No treat	12.106							
RR for progression = 2								
Treat all	12.232		12.188					
Test	12.176		12.223					
No test/No treat	12.106		12.032					
RR for death = 2								
Treat all	12.219		12.177					
Test	12.216		12.170					
No test/No treat	12.106		12.032					

Table 10: Psychosocial, legal and ethical impacts of testing

Issues that have an impact	Demented individuals (Scenario A)	Individuals with mild cognitive impairment (Scenario B)	Asymptomatic individuals with an elevated risk individuals (Scenario C)
Autonomy	-May aid in end-of-life decisions	-May aid in end-of-life decisions	-May aid in reproduction decisions
Non-maleficence	-Little benefit as current treatment is benign	-Little benefit as current treatment is benign -May promote depression	-Little benefit as current treatment is benign -May promote depression
Beneficence	-False negative may lead to failure to provide useful treatment	-False negative may lead to failure to provide useful treatment	-No impact since treatment is not otherwise given
Justice	-May create a "PET" barrier for treatment	-May create a "PET" barrier for treatment	-No impact since treatment is not otherwise given
Liability	-False negative may result in failure to treat	-False negative may result in failure to treat	-Minor liability for false negative as treatment is not otherwise given -False positive may introduce liability from damage due to labeling effect
Employability	-No impact since patients almost never employed	-Minor impact as patients are rarely employed	-Major potential impact
Insurability	-No impact as course is poor regardless of AD diagnosis	-Major potential impact	-Major potential impact

(Bowen, Teri, Kukull, et al., 1997; Doraiswamy, Steffens, Pitchumoni, et al., 1998; Drickamer and Lachs, 1992; Erde, Nadal, and Scholl, 1988; Holroyd, Snustad, and Chalifoux, 1996; Morris, Storandt, Miller, et al., 2001)

Figure 2: S-ROC curve



For details about studies 1-10, please refer to Table 9

Figure 3: Two Way Sensitivity Analysis
Mild Dementia

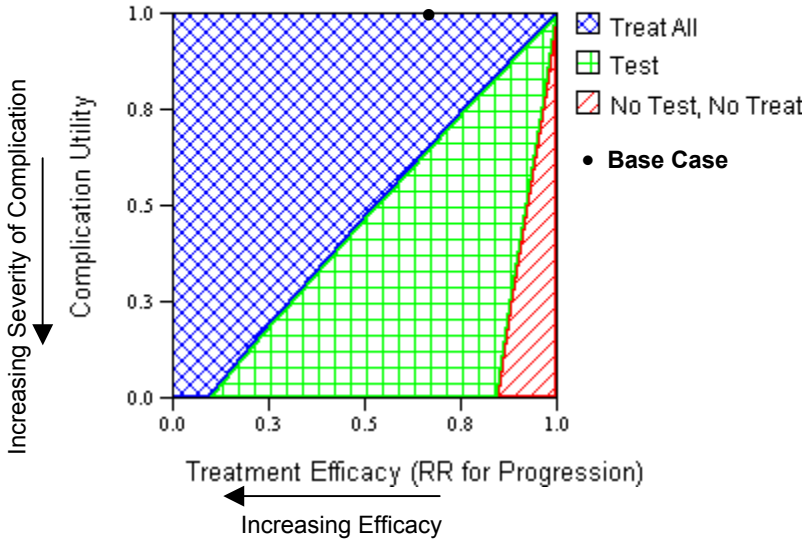


Figure 4: Two Way Sensitivity Analysis

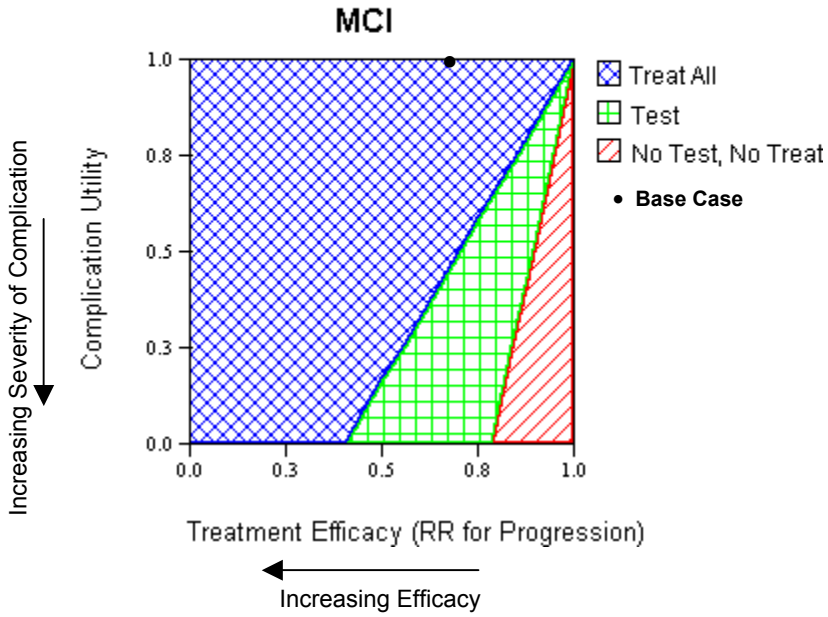


Figure 5a. Two Way Sensitivity Analysis

Asymptomatic, Elevated Risk

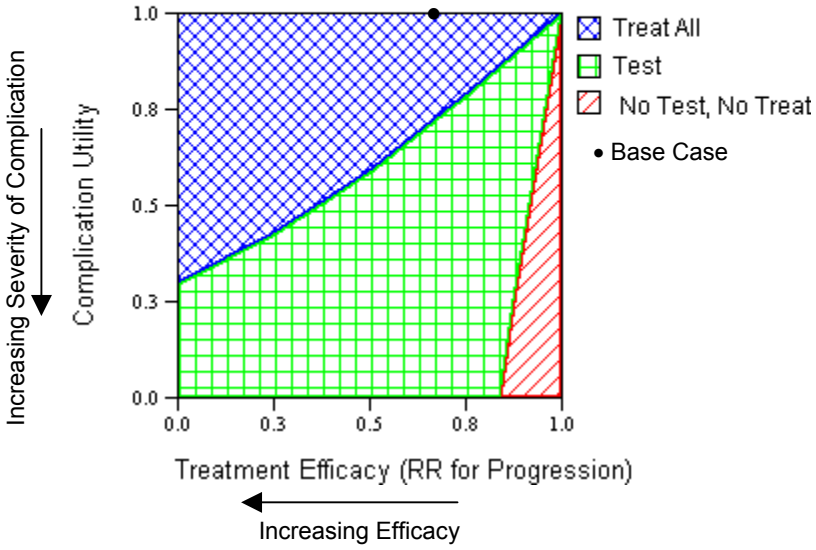


Figure 5b: One Way Sensitivity Analysis

Asymptomatic, Elevated Risk - Treatment Efficacy set at RR=0.8

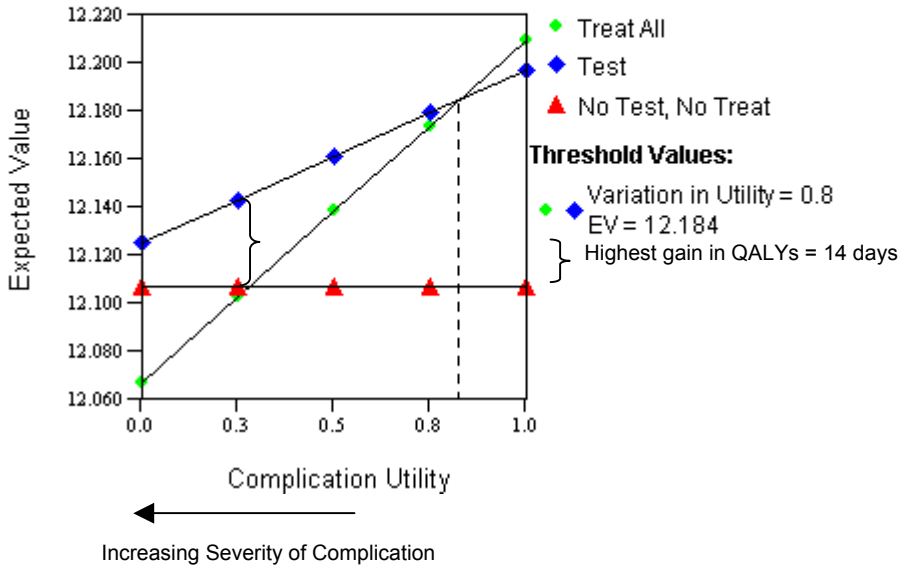
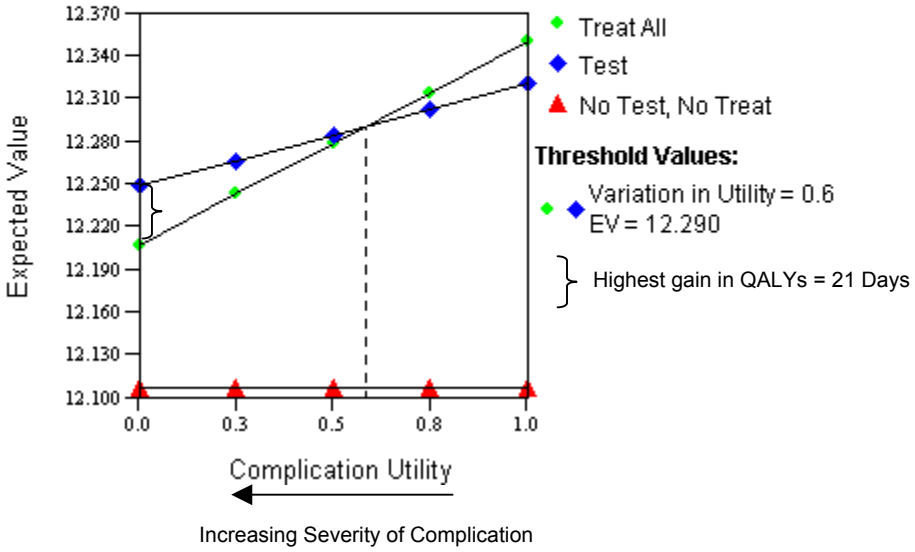


Figure 5c: One Way Sensitivity Analysis

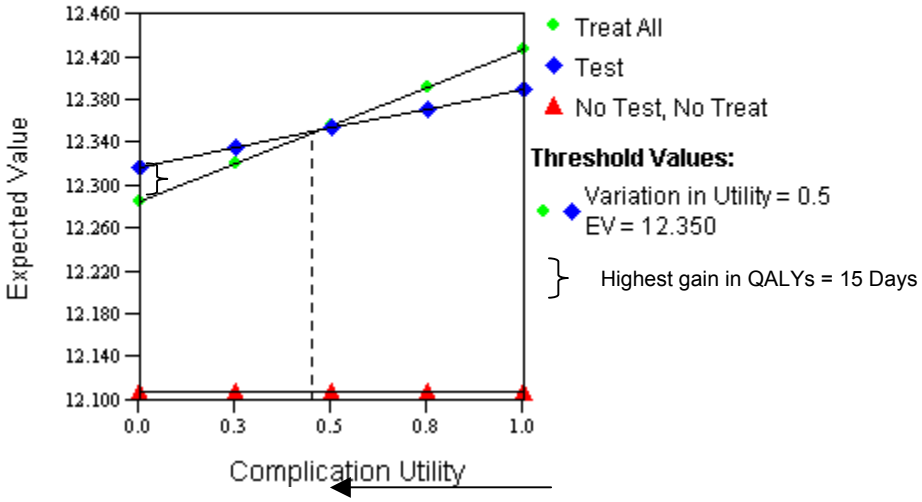
Asymptomatic, Elevated Risk - Treatment Efficacy set at RR=0.5



Increasing Severity of Complication

Figure 5d: One Way Sensitivity Analysis

Asymptomatic, Elevated Risk - Treatment Efficacy set at RR=0.3



Increasing Severity of Complication

Conclusions

Based on a comprehensive literature review, meta-analysis and decision analysis, we have the following four major conclusions regarding the use of PET in patients who may have AD:

1. For patients with dementia who have had a recommended clinical evaluation, treatment without further testing is superior to treating based on an additional test using PET. Since treatment for this clinical scenario has been shown to be moderately effective and relatively benign, the increase in true negatives (i.e. those who did not need the treatment) resulting from use of PET is overshadowed by the concomitant increase in false negatives (i.e. those who would benefit from the treatment, but for whom it would be withheld if they were not identified as positives).
2. If the evidence for treatment efficacy of AChE-I agents in patients with dementia can be extrapolated to patients with MCI, then empiric treatment of these patients would also be superior to treating based on PET. This is because the proportion of MCI patients with AD is comparable to – and may be higher than – the proportion of demented patients with AD. Even if survival is not improved, earlier treatment should improve the proportion of time a patient is alive with a lesser degree of impairment.
3. If the evidence for treatment efficacy of AChE-I agents in patients with dementia can be extrapolated to patients who are asymptomatic but have an elevated risk for AD, then empiric treatment of these patents would be superior to treating based on PET.

4. PET scanning could be of value if a new treatment were to be developed that was more effective but had a risk of one or more of a variety of highly negative consequences such as a reduction in quality of life, inducing progression of disease, or death.

There are two lines of speculation that suggest additional circumstances in which PET could be of value in patients who may have AD. The first line is that PET may identify a characteristic that predicts response to treatment beyond what can be predicted from clinical evaluation. However, we were unable to find trial or cohort studies to support this notion at this time.

The second line of speculation is that some patients, who should be treated with AChE-I agents but are not currently treated, *would* be treated if the physician were armed with an imaging study. While there is no support for this effect for PET in patients with dementia, there is support for the notion that a test – even a test of little or no incremental information value – can influence treatment behavior. However, it is quite possible that non-use of AChE-I agents would be unaffected by availability of PET if the decision to not treat with AChE-I medications is due, for example, to physician attitudes and beliefs (perhaps because they do not find the evidence supporting AChE-I medications compelling), financial considerations (out of pocket expenses for patients are onerous), or a combination (a perceived modest benefit is not worth the expense to the patient). In any case, if this value of testing is to be considered, it would be important to also consider the range of activities to improve clinician treatment practice.

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Abbreviations Used in the Evidence Tables

AD	Alzheimer's disease
DLB	Dementia with Lewy bodies
FDG	2-Fluro 2-deoxy D-glucose
FWHM	Full-width at half maximum
MBq	milli Bequerel
MCI	Mild Cognitive Impairment
MID	Multi-infarct dementia
MIX	Mixture of multi-infarct dementia and AD
MMSE	Mini-mental State Examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
No.	Number
NR	Not recorded
VD	Vascular dementia
vs.	versus
%	Percent

Evidence Table 1

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Azari, Pettigrew,Schapiro,Haxby, Grady, et al. (1993) #2140	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* NIH-Bethesda, Maryland *Setting:* AD/cognitive impairment clinic *PET characteristics:* • Scanner model- Scanditronix • Resolution- Atransverse 6mm, axial 11mm. • Acquisition mode- NR • Acquisition time- NR • Dose of FDG- NR • State of patient- eyes closed and ears plugged • Criteria for diagnosis- quanttative • Assessment- NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 41 AD- 19 - MCI: 0 - Mild-: 10 - Moderate: 9 Controls (normal)- 22 *Inclusion criteria:* NINCDS-ADRDA criteria for AD Controls: NR *Exclusion criteria:* Current depression, neurologic disease, radiologic evidence of pathology *Age (range):* AD-52-81 Controls-53-75 *Gender (male/female):* AD- 14/8 Controls1- 12/7 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. CONTROLS** Criteria for PET positivity: fronto-parietal hypometabolism PET+ 18 AD present, 1 AD absent, 18 Total PET- 1 AD present, 20 AD absent, 23 Total Total 19 AD present, 21 AD absent, 41 Total **SENSITIVITY: 94.7%** **SPECIFICITY: 95.2%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 0 • Test reader blinded- 0 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 1

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Burdette, Minoshima, Borght, Tran, Kuhl (1996) #1620	*Design:* case series, concomitant controls *Dates of data collection:* 1989-92 *Location:* Ann Arbor, MI *Setting:* NR *PET characteristics:* • Scanner model- CTI Knoxville, TN 931/08-12 scanner • Resolution- 7-7.5mm in plane, 7-8 mm axial • Acquisition mode- 2D and 3D • Acquisition time- 30min. • Dose of FDG- 10mCi(370MBq) • State of patient- NR • Criteria for diagnosis- quantitative • Assessment- blindly *Criteria for diagnosis of AD:* Clinical diagnosis	*No .of subjects:* total 79 AD- 39: - MCI and mild : 28 - Moderate-severe: 11 Controls1 (normal)-22 Controls2(cerebrovascular disease)-18 *Inclusion criteria:* NINCDS-ADRDA criteria for AD Controls: *Exclusion criteria:* any neurologic or psychiatric disorder or major illness *Age (mean +/-SD, range):* AD- 68+/-7.6(53-82) Controls1- 64+/-7.5 (52-76) Controls2-47+/-18(21-78) *Gender (male/female):* AD- 15/24 Controls1- 7/15 Controls2-7/11 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. non-demented CONTROLS** Criteria for PET positivity: symmetrical parieto-temporal hypometabolism AD present / AD absent / Total PET+ 33 / 5 / 38 PET- 6 / 35 / 41 Total 39 / 40 / 79 **SENSITIVITY: 85%** **SPECIFICITY: 88%** *2x2 table 2:* Sub-population studied: **QUESTIONABLE MILD AD vs non-demented controls** Criteria for PET positivity: symmetrical parieto-temporal hypometabolism AD present / AD absent / Total PET+ 22 / 5 / 28 PET- 6 / 35 / 41 Total 28 / 40 / 69 **SENSITIVITY: 79%** **SPECIFICITY: 88%** *2x2 table 3:* Sub-population studied: **MODERATE TO SEVERE AD (MMSE < 15)** Criteria for PET positivity: any hypometabolism AD present PET+ 11 PET- 0 Total 11 **SENSITIVITY: 100%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 1 • Results categorized by disease severity- 1 • Follow-up complete- 1 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 5

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Duara, Barker, Loewenstein et al. (1989) #3150	*Design*: case series, concomitant controls *Dates of data collection*: NR *Location:* Wien Ctr. For AD and Memory disorders, Mt.Sinai Med. Ctr., Miami beach, Fla *Setting*: AD center *PET characteristics:* Scanner model-PETT V Resolution-Image, in plane and axial: 15 mm. FWHM Acquisition mode-NR Acquisition time-30min. Dose of FDG-3-5 mCi State of patient-Eyes closed, blindfolded, in a quiet darkened room, resting Criteria for diagnosis-quantitative Assessment-done blindly *Criteria for diagnosis of AD*: Clinical diagnosis	*No. of subjects*: 152 AD-50 - MCI-NR - Mild-NR - Moderate-NR Severe-NR Controls1: young-29 Controls2: old-41 MID (multi-infarct-dementia) –17 MIX- 15 *Inclusion criteria*: Hachinski score for AD 0-4, MIX 5-7, MID >=8 *Exclusion criteria*: Pts. With neurological diagnoses other than AD, MID, MIX were excluded. Age (mean +/- SD): AD- 72.8 +/- 9.7 Controls1 (young)- 41.5 +/- 9.9 Controls2 (old)- 67.2+- 8.9 MID- 73.3+/-8 MIX- 74.3+/-8.8 *Gender (male/female*): NR *Race*: NR *Length of follow-up*: NR	*2x2 table 1*: Population studied: **AD vs. YOUNG NORMAL CONTROLS** Criteria for PET positivity: hypometabolism index AD present / Normal / Total PET+ 44 / 10 / 54 PET- 6 / 19 / 25 Total 50 / 29 / 79 SENSITIVITY: 88% SPECIFICITY: 65.5% *2x2 table 2:* Population studied: **AD vs. OLD NORMAL CONTROLS** Criteria for PET positivity: hypometabolism index AD present / Normal / Total PET+ 44 / 19 / 63 PET- 6 / 22 / 28 Total 50 / 41 / 91 SENSITIVITY: 88% SPECIFICITY: 53.6% *2x2 table 3*: Population studied: **AD vs. MID** Criteria for PET positivity: hypometabolism iindex AD present / Normal / Total PET+ 44 / 14 / 58 PET- 6 / 3 / 9 Total 50 / 17 / 67 SENSITIVITY: 88% SPECIFICITY: 17.6% *2x2 table 4*: Population studied: **AD vs. MIX** Criteria for PET positivity: hypometabolism index AD present / Normal / Total PET+ 44 / 12 / 56 PET- 6 / 3 / 9 Total 50 / 15 / 65 SENSITIVITY: 88% SPECIFICITY: 20%	*Quality score*: Representative sample-1 Setting/selection described-1 Scanner described-1 Standard criteria for interpretation-1 Test reader blinded-1 Results categorized by disease severity-0 Follow-up complete-0 Diagnosis confirmation done on the basis of long-term follow-up-0 *Total score*: 5

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Fazekas, Alavi, Chawluk, et al. (1989) #1170	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location*: Philadelphia, Pennsylvania *Setting*: AD/cognitive impairment clinic *PET characteristics:* Scanner model- PETT V Resolution- NR Acquisition mode- NR Acquisition time- NR Dose of FDG- NR State of patient- NR *Criteria for diagnosis*- qualitative *Assessment*- blindly *Criteria for diagnosis of AD:* Clinical diagnosis	*No. of subjects*: total 55 AD- 30: 24 probable, 6 possible - MCI: 0 - Mild-moderate: 14 - Moderate-severe: 16 Controls (normal)- 25 *Inclusion criteria:* Participants in an ongoing study of brain changes in normal aging and dementia NINCDS-ADRDA criteria for AD Controls: recruited from retirement communities or spouses of demented patients *Exclusion criteria*: NR *Age* (mean, range): AD- 65 (52-80) Controls- 65 (48-83) *Gender (male/female):* AD- NR Controls1- NR *Race:* AD- NR Controls- NR *Length of follow-up*: NR	*2x2 table 1*: Population studied: **AD vs. CONTROLS** Criteria for PET positivity: any hypometabolism AD present / AD absent / Total PET+ 27 / 4 / 31 PET- 1 / 21 / 22 Total 28 / 25 / 53 SENSITIVITY: 96% SPECIFICITY: 84% *2x2 table 2:* Sub-population studied: **MODERATE TO SEVERE AD (MMSE < 15)** Criteria for PET positivity: any hypometabolism AD present PET+ 14 PET- 1 Total 15 SENSITIVITY: 93% *2x2 table 3*: Sub-population studied: MILD TO MODERATE AD (MMSE > 15) Criteria for PET positivity: any hypometabolism AD present PET+ 13 PET- 0 Total 13 SENSITIVITY: 100%	*Quality score*: Representative sample- 1 Setting/selection described- 1 Scanner described- 1 Standard criteria for interpretation- 0 Test reader blinded- 1 Results categorized by disease severity- 1 Follow-up complete- 0 Diagnosis confirmation done on the basis of long-term follow-up- 0 *Total score*: 5

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Grady, Haxby, Schapiro, Gonzalez-Aviles, et al. (1990) #3160	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Bethesda, Maryland *Setting:* AD/cognitive impairment clinic *PET characteristics:* • Scanner model- SCANDITRONIX PC 1024-7B • Resolution- transverse 6mm, axial 10mm. • Acquisition mode- 2D • Acquisition time- 45min. • Dose of FDG- 5mCi • State of patient- eyes closed, ears plugged • Criteria for diagnosis- qualitative • Assessment- blindly *Criteria for diagnosis of AD:* Clinical diagnosis [7 AD patients had a histopathological confirmation of diagnosis]	*No.of subjects:* 74 AD- 33 MCI: NR Mild-moderate: NR Moderate-severe: NR Controls (normal)- 41 *Inclusion criteria:* NINCDS-ADRDA criteria for AD Controls: ruled out all systemic, psychiatric, neurologic disease, head trauma, drug abuse. *Exclusion criteria:* All other causes of dementia ruled out, no medication at time of study *Age (mean +/- SD):* AD- 68.5+/-9.5 Controls- 64.9+/-10.9 *Gender (male/female):* AD- 17/16 Controls1- 17/24 *Race:* AD- NR Controls- NR *Length of follow-up (mean+/- SD):* 11.9+/-7.5 months	*2x2 table 1:* Population studied: **AD vs. CONTROLS** Criteria for PET positivity: parieto-temporal hypometabolism |	AD present	AD absent	Total
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PET+	20	0	20
PET-	13	41	54
Total	28	41	69 | **SENSITIVITY: 61%** **SPECIFICITY: 100%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 1 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 4 *Notes:* Controls were considered negative for PET

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Herholz, Perani, Salmon, et al. (1993) #1140	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Germany, Italy, Belgium *Setting:* neurology clinics *PET characteristics:* • Scanner model- ECAT (Italy), NeuroECAT (Belgium), Scanditronix (Germany) • Resolution- inplane: 6 mm (Italy), 9.2 (Belgium), 7.8 (Germany) • Acquisition mode- NR • Acquisition time- 45 min (Italy & Belgium), 30 (Germany) • Dose of FDG- 250-300 MBq (Italy), 300 (Belgium), 185 (Germany) • State of patient- minimal sensory stimulation, eyes closed, ears without plugs, low noise room • Criteria for diagnosis- quantitative • Assessment- NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 71 AD- 37 - MCI: NR - Mild: NR - Moderate: NR - Severe: NR Controls (normal)- 34 *Inclusion criteria:* 40-80 year old NINCDS-ADRDA criteria for AD *Exclusion criteria:* NR *Age (mean ± SD):* AD-65.2 ± 7.4 Controls: - Italy 44.6 ± 15.7 - Belgium 58.2 ± 8.0 - Germany 65.4 ± 7.3 *Gender (male/female):* AD- 21/16 Controls: - Italy 5/5 - Belgium 5/5 - Germany 7/7 *Race:* NR AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. CONTROLS** Criteria for PET positivity: cut-off point at which sensitivity is 90% AD present / Controls / Total PET+ 33 / 5 / 38 PET- 4 / 28 / 32 Total 37 / 33 / 70 **SENSITIVITY: 89%** **SPECIFICITY: 85%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 0 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up-0 Total score: 2 *Notes:* to fill the 2x2 table, a cut point for the metabolic ratio at which sensitivity is 90% was selected

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Herholz, Adams, Kessler, et al., (1990) #3450	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Koln, Germany *Setting:* AD/cognitive impairment clinic *PET characteristics:* • Scanner model- Scanditronix PC-384 • Resolution- In plane resolution 7.8mm. FWHM • Acquisition mode- NR • Acquisition time- 30-40 min. • Dose of FDG- 185MBq(5mCi) • State of patient- Eyes closed, ears unplugged, darkened room, with low ambient noise. • Criteria for diagnosis- quantitative • Assessment- NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 38 AD- 19 Controls (normal)- 19 *Inclusion criteria:* NINCDS-ADRDA criteria for AD Controls: NR *Exclusion criteria:* NR *Age (mean +/-SD):* AD- 60.6+/-7.1 Controls- 61.1+/-10.2 *Gender (male/female):* AD- 3/16 Controls-9/10 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. CONTROLS** Criteria for PET positivity: any hypometabolism AD present / AD absent / Total PET+ 19 / 0 / 19 PET- 0 / 19 / 19 Total 19 / 19 / 38 **SENSITIVITY: 100%** **SPECIFICITY: 100%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 0 • Test reader blinded- 0 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 2

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Higuchi, Tashiro, Arai, et al. (2000) #590	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Tohoku University School of Medicine, Sendai, Miyagi 980, Japan *Setting:* outpatient clinic department of geriatric medicine, Parkinson's disease patient registry *PET characteristics:* • Scanner model-SET2400W, Shimadzu Inc., Japan • Resolution-spatial, 4 mm transaxial, 4.5 mm axial at FWHM at the center of the FOV • Acquisition mode-NR • Acquisition time-60 min • Dose of FDG-NR • State of patient-with minimal sensory stimulation, quite and dimly lit room, eyes open • Criteria for diagnosis-quantitative, metabolic ratios • Assessment-NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 28 Probable AD-11 - MCI: NR - Mild: NR - Moderate: NR - Severe: NR Controls1-Dementia with Lewy bodies (DLB): 7 Controls2-normal controls: 10 *Inclusion criteria:* NINCDS-ADRDA criteria for probable AD Consensus guidelines for DLB (McKeith) *Exclusion criteria:* NR *Age (mean ± SD):* AD- 66.5 ± 5.7 Controls1 (DLB)- 65.0 ± 8.8 Controls2 (Normal)- 65.0 ± 8 *Gender (male/female):* AD- 4/7 Controls1 (DLB)- 3/4 Controls2 (normal)- 4/6 *Race:* NR *Length of follow-up:* NR *MMSE (mean ± SD):* AD: 18.8 ± 3.3 months DLB: 16.1 ± 7.1 months	*2x2 table 1:* Population studied: **PROBABLE AD vs. DLB** Criteria for PET positivity: metabolic ratio, cut-off point of 0.92 AD present / DLB / Total PET+ 10 / 1 / 11 PET- 1 / 6 / 7 Total 11 / 7 / 18 **SENSITIVITY: 91%** **SPECIFICITY: 86%** *2x2 table 2:* Population studied: **PROBABLE AD vs. NORMAL CONTROLS** Criteria for PET positivity: metabolic ratio, cut-off point in order to obtain 90% sensitivity AD present / Normal / Total PET+ 10 / 7 / 17 PET- 1 / 3 / 4 Total 11 / 10 / 21 **SENSITIVITY: 91%** **SPECIFICITY: 30%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 0 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 2 *Notes:* to fill the 2nd 2x2 tables, a cut-off point for the metabolic ratio at which sensitivity is 90% was selected

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Ishii, Imamura, Yamaji, Sakamato, et al, (1998) #2610	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Himeji, Japan *Setting:* AD/cognitive impairment clinic *PET characteristics:* • Scanner model- Headtome IV(Shimadzu Corp.) • Resolution- NR • Acquisition mode- 3D • Acquisition time-12 min. • Dose of FDG- 185-259 MBq • State of patient- Eyes closed, with minimal sensory stimulation • Criteria for diagnosis- quantittative • Assessment- blindly *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 36 AD- 12 Controls1 (normal)- 12 Controls2 (Dementia with Lewy Bodies-DLB))- 12 *Inclusion criteria:* NINCDS-ADRDA criteria for AD Controls1: recruited from community, MMSE >28 Controls2:Consortium for DLB criteria *Exclusion criteria:* AD:Complications of other neurologic diseases, focal brain lesions on mRI, arterial occlusive lesions on cerebral and cranial MR angiography Controls:Abnormal findings on MRI *Age (mean +/-SD):* AD- 73.2+/-6.3 Controls1- 72.8+/-4.9 Controls2: 73.3+/-5.1 *Gender (male/female):* AD- 3/9 Controls1and 2- 3/9 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. Normal Controls** Criteria for PET positivity: any hypometabolism AD present / AD absent / Total PET+ 11 / 10 / 21 PET- 1 / 2 / 3 Total 12 / 12 / 24 **SENSITIVITY: 92%** **SPECIFICITY: 17%** *2x2 table 1:* Population studied: **AD vs. DLB** Criteria for PET positivity: any hypometabolism AD present / AD absent / Total PET+ 11 / 4 / 21 PET- 1 / 8 / 3 Total 12 / 12 / 24 **SENSITIVITY: 92%** **SPECIFICITY: 67%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 0 • Test reader blinded- 1 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 3

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Kippenhan, Barker, Pascal, et al. (1992) #1160	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Miami, Florida *Setting:* center for AD and memory disorders *PET characteristics:* • Scanner model- PETT V • Resolution- inplane and axial. 15 mm at FWHM • Acquisition mode- NR • Acquisition time- 30 min • Dose of FDG- 3-5 mCi • State of patient- eyes closed, blindfolded, quiet, darkened room • Criteria for diagnosis- qualitative • Assessment- blindly *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total: 91 Probable AD- 41 - MCI: NR - Mild: NR - Moderate: NR - Severe: NR Controls (normal)- 50 *Inclusion criteria:* NINCDS-ADRDA criteria for AD *Exclusion criteria:* NR *Age (mean ± SD):* Probable AD- 70.9 ± 8.8 Controls- 67.7 ± 8.9 *Gender (male/female):* AD- 21/20 Controls- 25/25 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. NORMAL CONTROLS** Criteria for PET positivity: any deficit present, cut-off point at which sensitivity is 90% AD present / AD absent / Total PET+ 37 / 15 / 52 PET- 4 / 35 / 39 Total 41 / 50 / 91 **SENSITIVITY: 90%** **SPECIFICITY: 70%** *2x2 table 2:* Population studied: **AD vs. NORMAL CONTROLS** Criteria for PET positivity: mild or greater deficit present, cut-off point at which sensitivity is 90% AD present / AD absent / Total PET+ 37 / 18 / 55 PET- 4 / 32 / 36 Total 41 / 50 / 91 **SENSITIVITY: 90%** **SPECIFICITY: 64%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 0 • Test reader blinded- 1 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 2 *Notes:* to fill the 2x2 table, a cut-off point for the metabolic ratio at which sensitivity is 90% was selected. We accepted 'any deficit' as the diagnostic criterion for PET positivity, which yielded a higher specificity.

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Messa, Perani, Lucignani, et al. (1994) #3300	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Milan, Italy *Setting:* NR *PET characteristics:* • Scanner model- Siemens • Resolution- 6.3mm full width at half maximum in axial plane • Acquisition mode- NR • Acquisition time-45 min • Dose of FDG- 250-300MBq • State of patient- eyes open, ears unplugged • Criteria for diagnosis- quantitative • Assessment- NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total: 31 Probable AD(mild to moderate)-21 Controls-normal subjects-10 *Inclusion criteria:* NINCDS-ADRDA criteria for AD *Exclusion criteria:* NR *Age (mean ± SD):* AD- 62.8 ± 7.8 Controls-47+/-13 *Gender (male/female):* AD- 10/11 Controls- 3/7 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. NORMAL CONTROLS** Criteria for PET positivity: out of mean +/- 2 SD AD present AD absent Total PET+ 21 1 22 PET- 0 9 9 Total 21 10 31 **SENSITIVITY: 100%** **SPECIFICITY: 90%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 0 • Test reader blinded- 0 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 1

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Mielke, Pietrzyk, Jacobs, et al. (1994) #540	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Koln, Germany *Setting:* Neurology clinic *PET characteristics:* • Scanner model- Siemens ECAT • Resolution- Image, transaxial :>6mm, axial :5mm at the center • Acquisition mode- NR • Acquisition time-NR • Dose of FDG- 370MBq • State of patient- Eyes closed, with minimal sensory stimulation • Criteria for diagnosis- quantittative • Assessment- blindly *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 45 AD- 10 Controls1 (normal)- 13 Controls2 (Vascular Dementia)- 12 *Inclusion criteria:* NINCDS-ADRDA criteria for AD Modified Hachinski score <=2 *Exclusion criteria:* NR *Age (mean +/-SD):* AD- 68.8+/-5.6 Controls1- 59.5+/-11.1 Controls2: 69.0+/-9.4 *Gender (male/female):* AD- 14/6 Controls1- 6/6 Controls2: 5/8 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. NORMAL CONTROLS** Criteria for PET positivity: cut off point at which sensitivity is 90% |	AD present	AD absent	Total | | PET+ | 18 | 5 | 23 | | PET- | 2 | 8 | 10 | | Total | 20 | 13 | 33 | **SENSITIVITY: 90%** **SPECIFICITY: 62%** *2x2 table 2:* Population studied: **AD vs. VASCULAR DEMENTIA** Criteria for PET positivity: cut off point at which sensitivity is 90% |	AD present	AD absent	Total | | PET+ | 18 | 5 | 23 | | PET- | 2 | 7 | 9 | | Total | 20 | 12 | 32 | **SENSITIVITY: 90%** **SPECIFICITY: 58%**	*Quality score:* • Representative sample- 1 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 0 • Test reader blinded- 1 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 3 *Notes:* to fill in the 2*2 tables, a cut point for the metabolic ratio at which sensitivity is 90% was selected

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Minoshima, Kirk, Foster, et al. (1995) #2170	*Design:* case series, concomitant controls *Dates of data collection:* 1989-1992 *Location:* Michigan *Setting:* AD/cognitive impairment clinic *PET characteristics:* • Scanner model- Siemens ECAT • Resolution- 8mm full width at half maximum • Acquisition mode- NR • Acquisition time- 30 min. • Dose of FDG- 370 MBq • State of patient- quiet, dimly lit room. • Criteria for diagnosis- quantitative • Assessment- NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 59 Probable AD- 37 Controls (normal)- 22 *Inclusion criteria:* NINCDS-ADRDA criteria for AD Controls: No history of neurological or psychiatric disorder, normal neurologic exam. *Exclusion criteria:* NR *Age (mean +/-SD):* AD- 64 +/- 8 Controls- 68 +/- 7 *Gender (male/female):* AD- NR Controls- NR *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **Probable AD vs. CONTROLS** Criteria for PET positivity: Glucose metabolic rate of parieto-temporal cortex AD present / AD absent / Total PET+ 36 / 0 / 36 PET- 1 / 22 / 23 Total 37 / 22 / 59 **SENSITIVITY: 97%** **SPECIFICITY: 100%**	*Quality score:* • Representative sample- 1 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 0 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 4

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Ohyama,Senda, Mishina, et al. (2000) #1250	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Tokyo,Japan *Setting:* AD/cognitive impairment clinic *PET characteristics:* • Scanner model- Headtome 4 • Resolution- NR • Acquisition mode- NR • Acquisition time- NR • Dose of FDG- NR • State of patient- NR • Criteria for diagnosis- quantitative • Assessment-NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 31 AD- 21 - MCI: NR - Mild- - Moderate: NR - Severe: NR Controls (normal)- 10 *Inclusion criteria:* NR Controls: NR *Exclusion criteria:* NR *Age (mean +/-SD):* AD- 61 +/-10 Controls- 55 +/-12 *Gender (male/female):* AD- NR Controls1- NR *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. CONTROLS** Criteria for PET positivity: any hypometabolism AD present / AD absent / Total PET+ 18 / 1 / 19 PET- 3 / 9 / 12 Total 21 / 10 / 31 **SENSITIVITY: 86%** **SPECIFICITY: 90%**	*Quality score:* • Representative sample- 1 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 0 • Test reader blinded- 1 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 4 *Notes:* Threshold value of uptake in the parietal lobe was set as 5.

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Szelies, Mielke, Herholz, Heiss. (1994) #2010	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Cologne, Germany *Setting:* AD/cognitive impairment clinic *PET characteristics:* • Scanner model- Scanditronix 384 • Resolution- NR • Acquisition mode- 2D • Acquisition time- 20min. • Dose of FDG- 185mBq(5mCi) • State of patient- ears unplugged, darkened room, low ambient noise • Criteria for diagnosis- quantitative • Assessment- NR *Criteria for diagnosis of AD:* Clinical diagnosis	*No.of subjects:* total 58 AD probable: 24 -MCI: NR -Mild: 14 -Moderate: 10 Controls1 (normal)- 15 Controls2-Vascular dementia – 19 -Mild:12 -Moderate:7 *Inclusion criteria:* NINCDS-ADRDA criteria for probable AD Vascular dementia- modified Hachinsky score >=4 Controls: MMSE scores>=28 *Exclusion criteria:* depression or other mental disorders *Age (mean, range):* AD- 65.9+/-7.6 Controls1-60+/-7.3 Controls2- 68.5+/-9.77 *Gender (male/female):* AD- 10/14 Controls1- 8/7 Controls2- 14/5 *Race:* AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. VD** Criteria for PET positivity: metabolic ratio AD present / AD absent / Total PET+ 18 / 9 / 27 PET- 6 / 10 / 16 Total 24 / 19 / 43 **SENSITIVITY: 75%** **SPECIFICITY: 53%** *2x2 table 2:* Sub-population studied: **AD vs NORMAL** Criteria for PET positivity: any hypometabolism AD present / AD absent PET+ 18 / 5 PET- 6 / 10 Total 24 / 15 **SENSITIVITY: 75%** **SPECIFICITY: 67%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 0 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 0 • Results categorized by disease severity- 0 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 2

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Hoffman, Welsh-Bohmer, Hanson, Crain, et al. (2000) #1000	*Design:* case series, concomitant controls *Dates of data collection:* NR *Location:* Durham, NC *Setting:* center for AD *PET characteristics:* • Scanner model- ECAT III (CTI, Knoxville, TN), or GE4096 Plus • Resolution- NR • Acquisition mode- 2D • Acquisition time- NR min • Dose of FDG- 370mBq(10mCi) • State of patient- with minimal sensory stimulation • Criteria for diagnosis- qualitative • Assessment- blindly *Criteria for diagnosis of AD:* Histopathological diagnosis	*No.of subjects:* total: 22 Probable AD- 16 - MCI: NR - Mild: NR - Moderate: NR - Severe: NR Controls (normal)- 6 *Inclusion criteria:* NINCDS-ADRDA criteria for AD, diagnostically challenging memory loss, pathologic confirmation of diagnosis *Exclusion criteria:* NR *Age (mean ± SD):* Probable AD- 66.4(54-77) Controls- 62.5(37-80) *Gender (male/female):* AD- 10/6 Controls- 5/1 *Race:* AD- NR Controls- NR *Length of follow-up:* 24.9 months+/- 28.1 months	*2x2 table 1:* Population studied: **AD vs. Other causes of dementia** Criteria for PET positivity: any deficit present, cut-off point at which sensitivity is 90% |	AD present	AD absent	Total
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PET+	14	2	16
PET-	2	4	6
Total	16	6	22 | **SENSITIVITY: 87.5%** **SPECIFICITY: 66.7%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 1 • Results categorized by disease severity- 0 • Follow-up complete- 1 • Diagnosis confirmation done on the basis of long-term follow-up- 1 Total score: 6

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Salmon, Sadzot, Maquet, et al. (1994) #1090	*Design:* case series, concomitant controls *Dates of data collection:* RN *Location:* Liège, Belgium *Setting:* patients referred for PET for differential diagnosis *PET characteristics:* • Scanner model- Neuro ECAT • Resolution- transverse 12.4 mm, axial 15 mm, at FWHM • Acquisition mode- NR • Acquisition time- 40 min • Dose of FDG- 8 mCi • State of patient- resting, minimal noise, eyes closed • Criteria for diagnosis- quantitative • Assessment- blindly *Criteria for diagnosis of AD:* Clinical diagnosis [5 AD patients had a histopathological confirmation of diagnosis]	*No. of subjects:* total 129 AD- 65 - MCI: 0 - Mild: 16 - Moderate: 25 - Severe: 24 Controls- 64 (19 degenerative dementias + 45 other dementias) *Inclusion criteria:* Patients referred for differential diagnosis of dementia NINSA-ADRA criteria for AD *Exclusion criteria:* NR *Age (mean ± SD):* AD- 65.9 ± 7.4 Controls (degenerative dementia)- 59.5 ± 10.6 *Gender (male/female):* AD- NR Controls- NR *Race:* NR AD- NR Controls- NR *Length of follow-up:* NR	*2x2 table 1:* Population studied: **AD vs. NON-AD DEMENTIAS** Criteria for PET positivity: Temporo-parietal bilateral or unilateral AD present / Non-AD dementia / Total PET+ 56 / 25 / 81 PET- 9 / 39 / 47 Total 65 / 64 / 128 **SENSITIVITY: 86%** **SPECIFICITY: 61%** *Sensitivities for sub-groups of AD* Sub-population studied: **MILD AD** AD present PET+ 12 PET- 4 Total 16 **SENSITIVITY: 75%** Sub-population studied: **MODERATE AD** AD present PET+ 22 PET- 3 Total 25 **SENSITIVITY: 88%** Sub-population studied: **SEVERE AD** AD present PET+ 22 PET- 2 Total 24 **SENSITIVITY: 92%**	*Quality score:* • Representative sample- 1 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 1 • Results categorized by disease severity- 1 • Follow-up complete- 0 • Diagnosis confirmation done on the basis of long-term follow-up- 0 Total score: 6

Study	Design and PET characteristics	Patient population	Results	Quality Score/Notes
Silverman D, Small G, Chang C, et al. (2001) #4250	*Design:* case series *Dates of data collection:* 1984-2000 *Location:* Los Angeles, CA, Berkeley, CA, Bethesda, MD, Durham, NC, Philadelphia, PA, Liège, Belgium, Köln, Germany *Setting:* centers for AD *PET characteristics:* • Scanner model- Siemens/CTI ECAT 831 or 931, ECAT EXACT HR or HR+ (CTI, Knoxville, TN) in California. NR for other centers • Resolution- NR • Acquisition mode- NR for each center • Acquisition time- 40 min in California, NR for other centers • Dose of FDG- 10 mCi or 370 MBq in California, NR for other centers • State of patient- eyes open in a dimly lit, quiet room in California, NR for other centers • Criteria for diagnosis- progression = (1) focal cortical hypometabolism in parietal, temporal, and/or frontal lobes, or (2) diffuse hypometabolism in associative cortex with relative sparing of sensorimotor cortex, or (3) a pattern of cerebral metabolism pathognomonic for a known neurodegenerative disease associated with progressive cognitive decline • Assessment- blind Criteria for diagnosis of AD: Histopathological diagnosis	*No. of subjects:* 97 with pathologically confirmed diagnosis of AD - 41 patients with questionable or mild dementia at time of diagnosis Controls – 23 patients with other pathologically confirmed diagnosis of dementia, 16 patients without confirmed cause of dementia at autopsy - 14 patients with questionable or mild dementia at time of diagnosis *Inclusion criteria:* Patients evaluated with PET and who had subsequent neuropathological examination *Exclusion criteria:* NR *Age (mean ± SD):* NR *Gender (male/female):* AD- NR Controls- NR *Race:* AD- NR Controls- NR *Length of follow-up:* autopsies performed an average of 2.9 years after PET (range- 0.1-9.5 years)	*2x2 table 1:* Population studied: **AD confirmed by autopsy vs. Other causes of dementia/no cause of dementia** Criteria for PET positivity: Hypometabolism AD present / AD absent / Total PET+ 91 / 11 / 102 PET- 6 / 30 / 36 Total 97 / 41 / 138 **SENSITIVITY: 93.8%** **SPECIFICITY:73.2%** *2x2 table 2:* Population studied: **Patients with questionable or mild dementia at time of PET, AD confirmed by autopsy vs. Other causes of dementia/no cause of dementia** Criteria for PET positivity: Hypometabolism AD present / AD absent / Total PET+ 39 / 4 / 43 PET- 2 / 10 / 12 Total 41 / 14 / 55 **SENSITIVITY: 95.1%** **SPECIFICITY:71.4%** *2x2 table 3:* Population studied: **Patients with moderate to severe dementia at time of PET, AD confirmed by autopsy vs. Other causes of dementia/no cause of dementia** Criteria for PET positivity: Hypometabolism AD present / AD absent / Total PET+ 52 / 7 / 59 PET- 4 / 20 / 24 Total 56 / 27 / 83 **SENSITIVITY: 92.8%** **SPECIFICITY: 74.1%**	*Quality score:* • Representative sample- 0 • Setting/selection described- 1 • Scanner described- 1 • Standard criteria for interpretation- 1 • Test reader blinded- 1 • Results categorized by disease severity- 0 • Follow-up complete- 1 • Diagnosis confirmation done on the basis of long-term follow-up- 1 Total score: 6

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Appendix A: American Academy of Neurology Guidelines

Practice Parameter: Diagnosis of dementia (an evidence-based review)
Report of the Quality Standards Subcommittee of the American Academy of Neurology

The recommendations made are –

1. The DSM-III-R definition of dementia is reliable and should be used (Guideline)
2. The National Institute of Neurologic, Communicative Disorders and Stroke-ADD and Related Disorders Association (NINCDS-ADRDA) or the Diagnostic and Statistical manual, 3rd edition, revised (DSM-IIIR) diagnostic criteria for AD and clinical criteria for Creutzfeldt-Jacob disease (CJD) have sufficient reliability and validity and should be used (Guideline). Diagnostic criteria for vascular dementia, dementia with Lewy bodies, and frontotemporal dementia may be of use in clinical practice (Option) but have imperfect reliability and validity.
3. Structural neuroimaging with a non-contrast CT or MR scan in the initial evaluation of dementia is appropriate. Because of insufficient data on validity, no other imaging procedure is recommended (Guideline). There are no currently genetic markers recommended for routine diagnostic purposes (Guideline). The CSF 14-3-3 protein is useful for confirming or rejecting the diagnosis of CJD (Guideline).
4. Screening for depression, B12 deficiency, and hypothyroidism should be performed (Guideline). Screening for syphilis in patients with dementia is not justified unless clinical justification for neurosyphilis is present (Guideline).

(Knopman, DeKosky, Cummings, et al., 2001)

Appendix B: Definitions

1. Dementia – *The Diagnostic and Statistical Manual* (DSM-IV) (McKhann, Drachman, Folstein, et al., 1984) of the American Psychiatric Association requires that for a diagnosis of dementia the diagnostic criteria of – "the development of multiple cognitive deficits that include memory impairment and at least one of the following: aphasia, apraxia, agnosia, or a disturbance in executive functioning".

2. Mild Cognitive Impairment- Mild cognitive impairment refers to the clinical state of individuals who are memory impaired but are otherwise functioning well and do not meet clinical criteria for dementia (Petersen, Stevens, Ganguli, et al., 2001).

3. Alzheimer's disease – In 1984, the Work Group convened by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) published criteria that standardized the diagnosis of AD (McKhann, Drachman, Folstein, et al., 1984) –
   In a demented person, *probable* AD is present when dementia is characterized by gradual onset and progression and when other systemic or brain disorders that potentially could cause dementia are absent. *Possible AD* is diagnosed if there are variations in the presentation or course of dementia or when other potentially dementing disorder (e.g., stroke) is present but is believed not to be responsible for dementia. The term *definite* AD is reserved for cases of clinically diagnosed AD in which there is histopathological confirmation by cerebral biopsy or autopsy.

4. Staging Instruments for Alzheimer's disease - Several clinical rating scales can be used to provide a global measure of the severity of dementia. They are sensitive indicators of cognitive change. The Clinical Dementia Rating is a five point ordinal scale, assesses cognitive ability by structured informant interview and patient testing in six domains with individual descriptors for each level of severity in each domain. The Global Deterioration Scale (GDS) and the CAMDEX are other instruments that can also be used.
   We have used the CDR scale, since this is the scale that the CERAD has utilized to grade its patients, and since that is the data set that we have used in some parts of our analysis. This scale designates 1 as mild dementia, 2 as moderate and 3 as severe dementia. (Appendix C)

Mild dementia (CDR stage 1) – Memory impairment in these individuals interferes with their daily activities. There are growing difficulties handling complex problems and managing independence in household responsibilities and daily activities (Scinto and Daffner,2000).

Moderate dementia (CDR stage 2) – These individuals exhibit significant memory loss, frequent disorientation, impairment of social judgment, and an increasing need for supervision in their daily living activities (Scinto and Daffner,2000).

Severe dementia (CDR stage 3 and beyond) – Patients are totally dependent on others for personal care and everyday problem solving (Scinto and Daffner, 2000; McKhann, Drachman, Folstein, et al., 1984; Petersen, Stevens, Ganguli, et al., 2001).

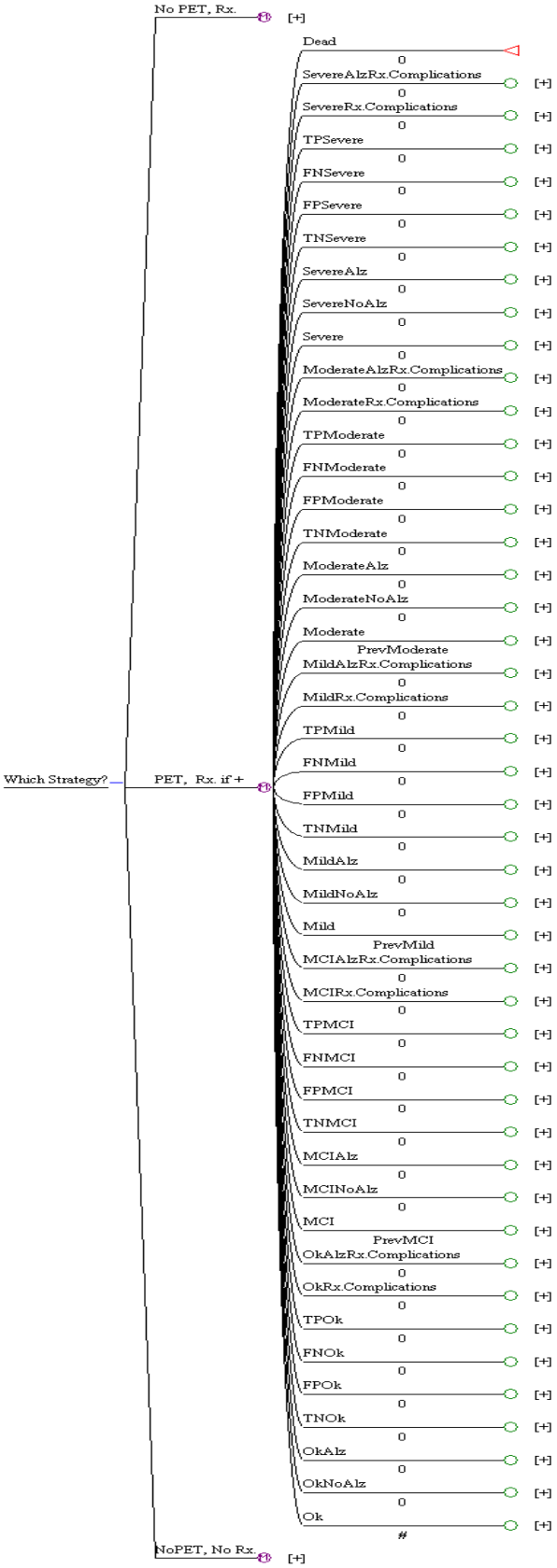
Appendix C: Clinical Dementia Rating (CDR)

Impairment					
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relation-ships; oriented for place at examination; may have geo-graphic disorientation elsewhere	Severe difficulty with time relation-ships; usually disoriented in time, often to place	Oriented to person only
Judgment & problem solving	Solves everyday problems well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, business and financial affairs, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home	
				Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home & hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly sustained	No significant function in home
Personal care	Fully capable of self care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Appendix C (ctd).

Note: Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.
From Berg, L. Mild senile dementia of the Alzheimer type. In: Elizan, T.S., ed. Parkinson's Disease, Alzheimer's Disease, and the Aging Brain, Mt. Sinai Journal of Medicine, Vol. 55, pp. 87-96, 1988.

Appendix D: Markov model



Appendix E: Data Abstraction Form

PET SCANNING FOR ALZHEIMER'S DISEASE

Reviewer: _____ First Author & Year: _____ _____ ProCite # _____

STUDY DESIGN (check one):

_____ RCT
Randomization method: Sealed envelope _____
Date/Chart # _____
Not described _____

Other _____ Describe:

_____ Cohort
_____ Case Series, no controls, n = _____
_____ Case Series, historical controls, n = _____
_____ Case Series, concomitant controls, n = _____
_____ Not Specified or unable to classify

STUDY LOGISTICS:
Inclusive dates of data collection (specify month and year):

From _____ to _____

Geographic Location (in US give city and state; outside of US give city and country):
_____

PATIENT POPULATION:

N = _____ Clarify as needed:

Study Setting**:** (check all that apply)
_____ Inpatient
_____ General outpatient clinics/ physician office
_____ Neurologist clinic/office
_____ Alzheimer's/ Cognitive impairment clinic
_____ Not specified or unable to determine
_____ Other Describe:

Inclusion Criteria (briefly describe):

Exclusion Criteria (briefly describe):

PET TECHNICAL CHARACTERISTICS :

(A) Scanner type -
Dedicated / Coincident / Camera-based

(B) Scanner Model -
GE advanced / Siemens ECAT / Siemens ECAT HR / Seimens EXACT HR plus / any other

(C) Resolution specified–
Intrinsic / Image / both / neither mentioned
Details of resolution (numerical values): _____

(D) Acquisition mode -
2-D / 3-D / not mentioned

(E) Acquisition time -
____ / Not mentioned

(F) Injected dose of FDG -
____ **/** Not mentioned

(G) State of patient during testing -
With minimal sensory stimulation / Eyes closed and ears plugged / any other circumstances /not mentioned

CRITERIA USED FOR DIAGNOSIS OF AD :

PET done -
Qualitatively / Quantitatively / not mentioned

Criteria used for diagnosis - Bilateral, symmetrical, posterior parietal hypo metabolism /
Bilateral asymmetrical, posterior parietal hypo metabolism /
unilateral, posterior parietal hypo metabolism

ASSESSMENT :

Done blindly / not done blindly / not mentioned

SUBJECT CHARACTERISTICS:

1) Specify Control Group

2) Use "NR" to indicate "Not reported"

	Control Group	**AD group**
Age:		
Mean		
SD		
Median		
Range		
Race: White	n = / %	n = / %
Black	n = / %	n = / %
Hispanic	n = / %	n = / %
Other	n = / %	n = / %
Gender: Male	n = / %	n = / %
Female	n = / %	n = / %
No.:		
OK	n = / %	n = / %
MCI	n = / %	n = / %
Mild dementia	n = / %	n = / %
Moderate dementia	n = / %	n = / %
Severe dementia	n = / %	n = / %
Length of follow-up:		
Mean		
SD		
Median		
Range		

RESULTS

(Use 1 sheet for each combination of population and positivity criteria)

Population/subpopulation studied: _____

Criterion for PET positivity: _____

Criterion for diagnosis of AD: Clinical diagnosis / Histopathological

	AD present	AD absent	Total
PET positive			
PET negative			
Total			

Sensitivity –

Specificity –

Prevalence –

Use space below to develop a table:

SCORE FOR PAPER:

(Please assign a score of 0 if the paper did not adequately meet the criterion, or if the data was inadequate to determine the criterion, and assign a score of 1 if the paper met the criterion.)

1. The study had a representative sample of patients with an appropriate spectrum of disease. 0 / 1
2. The setting and selection of the population under investigation was clearly described. 0 / 1
3. The scanner model (pg. 2, A) or the type and the resolution of the scanner (pg. 2, B and C) were mentioned. 0 / 1
4. Standard criteria were used for test interpretation. (see pg. 2) 0 / 1
5. The test reader and the person assigning reference standard diagnosis was blinded. 0 / 1
6. The results were categorized by disease severity. 0 / 1
7. The follow-up was complete (no verification bias). 0 / 1

8. Histopathological or clinical confirmation was done on the basis of a long-term (>=one year) follow-up with standard criteria. 0 / 1

Total score =

PAPER RATING –

(<4=POOR, 4-6 = FAIR, >7 = GOOD)

POOR / FAIR / GOOD

Page nos. from the article used to develop table data –

Notes -