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SPECT perfusion imaging in the diagnosis of Alzheimer's disease

A clinical-pathologic study

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Article abstract—*Objective:* Numerous studies have suggested that temporoparietal hypoperfusion seen on brain imaging with SPECT may be useful in diagnosing AD during life. However, these studies have often been limited by lack of pathologic validation and unrepresentative samples. The authors performed this study to determine whether SPECT imaging provides diagnostically useful information in addition to that obtained from a clinical examination. *Methods:* Clinical data and SPECT images were collected prospectively, and patients were followed to autopsy. Clinical history, pathologic findings, and SPECT images were each evaluated by raters blind to other features, and clinical and SPECT diagnoses were compared with pathologic diagnoses. The study population consisted of 70 patients with dementia, followed to autopsy; 14 controls followed to autopsy; and 71 controls (no autopsy performed). The primary outcome was the likelihood of a pathologic diagnosis of AD given a positive clinical diagnosis, a positive SPECT diagnosis, and both. *Results:* When all participants (patients and controls) were included in the analysis, the clinical diagnosis of “probable” AD was associated with an 84% likelihood of pathologic AD. A positive SPECT scan raised the likelihood of AD to 92%, whereas a negative SPECT scan lowered the likelihood to 70%. SPECT was more useful when the clinical diagnosis was “possible” AD, with the likelihood of 67% without SPECT, 84% with a positive SPECT, and 52% with a negative SPECT. Similar results were found when only patients with dementia were included in the analysis. *Conclusions:* In the evaluation of dementia, SPECT imaging can provide clinically useful information indicating the presence of AD in addition to the information that is obtained from clinical evaluation.

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Despite intense efforts aimed at developing laboratory markers for specific dementing illnesses, establishing the cause of dementia during life remains a clinical process. Because clinical diagnostic criteria for AD¹ generally perform with high positive predictive value relative to the current pathologic “gold

standard” in research settings,² laboratory diagnostic tests need to meet a relatively high standard to be accepted. Functional brain imaging using SPECT to evaluate cerebral perfusion is a laboratory investigation that has been proposed as useful in the diagnosis of dementia. Although many studies have found

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that the pattern of temporal and parietal hypoperfusion has high sensitivity, specificity, and positive and negative predictive value for discriminating patients with AD from healthy older subjects,³⁻⁵ most studies have suffered to varying extent from lack of pathologic validation or highly selected and screened patients, limiting the validity and generalizability of the findings.

In 1988, the Oxford Project to Investigate Memory and Aging (OPTIMA) began a longitudinal prospective study, enrolling a cohort of patients with dementia who underwent clinical evaluation, SPECT perfusion imaging, annual reevaluation, and, ultimately, autopsy. The results of applying a specific set of SPECT diagnostic criteria were originally reported in the first 105 cases to come to postmortem.⁶ We now report the results of an independent, blinded evaluation of SPECT imaging that includes some of this cohort of subjects with dementia, all of whom had neuropathologic verification of the cause of dementia, in addition to a group of control subjects, some of whom also had neuropathologic evaluation at autopsy. The study was designed to determine the accuracy of the premortem diagnosis of AD using SPECT perfusion imaging, and also to determine the additional benefit, over and above a clinical evaluation, that SPECT may confer.

Methods. *Patient selection.* A total of 158 subjects meeting inclusion and exclusion criteria were imaged with SPECT during the time period of this project. Although recruitment for the OPTIMA study began in 1988, in November 1992 SPECT instrumentation was upgraded. Because of the superior quality of SPECT images obtained after this upgrade, and to ensure comparability of scans and high quality of images, only subjects who were scanned on this instrument were included in this study. Subjects were included in this series if they were scanned on this instrument between November 1992 and the conclusion of the project in 1996 and also had pathologic postmortem examination of the brain. For the purposes of this study, initial evaluation was taken as the time of the first SPECT scan on this scanner.

Patients were referred to the study from both community and institutional settings by health care practitioners who were aware of the ongoing research project. Referrals were obtained from a host of different medical specialists (geriatric psychiatrists, neurologists, general practitioners, and geriatricians), along with community organizations, social service agencies, and local advertisements. Subjects were included if they had documented cognitive loss as determined using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX),⁷ had a reliable informant, could tolerate small doses of benzodiazepines for sedation (if necessary), and were willing to participate in all aspects of the longitudinal study. Exclusionary criteria included only the presence of very late stage dementia. Specific dementia diagnoses were neither inclusion nor exclusion criteria, nor were specific psychiatric diagnoses (e.g., depression). Subjects were permitted to take any additional medications at the time of enrollment or during the study, including those that might have CNS effects. At

the time of the study, cholinergic therapy was generally unavailable in the United Kingdom and was not used in any of the subjects enrolled in this series. All medication use was recorded.

Control subjects were volunteers from the community, including spouses of patients with dementia and those recruited through advertisement or word of mouth. Identical exclusion and inclusion criteria were applied to the control subjects, except that they had no evidence of cognitive dysfunction or memory complaints. Procedures for obtaining informed consent from both patients and controls were approved by both the Central Oxford Research and Psychiatric Sector Research Ethics Committees.

Clinical evaluation and follow-up. At the time of enrollment, all patients and controls underwent an extensive evaluation that included the CAMDEX, history and physical examination, routine blood tests, lumbar puncture, and CT and SPECT brain imaging. At the conclusion of the evaluation, a clinical diagnosis was established and patients were enrolled for follow-up. The evaluation was repeated annually, unless a patient died, withdrew from the study, or was too ill to undergo the evaluations. Autopsy consent was often requested in life and reconfirmed at death using a carefully constructed protocol as previously reported.⁸

SPECT imaging. SPECT imaging was performed using single-headed rotating scanner (General Electric 400XCT) and the perfusion radiotracer ^{99m}Tc exametazime (Ceretek, Amersham International, Amersham, UK). Each subject was prepared with a 22-gauge IV catheter, and 500 MBq was injected IV, followed by a 5-mL saline flush while the subject sat in a quiet waiting area with subdued light. SPECT imaging began approximately 30 minutes following tracer injection. Data were acquired as 64 images over 360°, with each image having an acquisition time of 20 seconds and a 64 × 64 matrix. At the time of the studies, patients and controls with behavioral difficulties or anxiety were rarely given low doses of diazepam after the uptake period of the tracer.

Neuropathology. Within 24 to 48 hours of death, the brain was removed and suspended in buffered neutral formalin for at least 6 weeks. Histologic sections were taken from the frontal, temporal, and parietal neocortex, hippocampus, cerebellum, midbrain, and pons. The sections were stained with hematoxylin and eosin, congo red, Luxol fast blue, and cresyl violet, and with methenamine silver and Cross's modification of the Palmgren stain to demonstrate argyrophilic plaques and neurofibrillary tangles. Neuropathologic reports were prepared describing the density and distribution of neurofibrillary tangles and neuritic plaques. Specific neuropathologic criteria included those described by Khachaturian⁹ and those proposed by the Consortium to Establish a Registry for AD (CERAD).¹⁰ Other causes of dementia were diagnosed according to standard neuropathologic criteria available at the time.

Clinical, pathologic, and imaging interpretation. To ensure that clinical and imaging diagnoses were arrived at independently, separate raters evaluated both aspects of the study. A single individual (W.J.J.) reviewed all clinical protocols, which consisted of clinical history, physical examination, and cognitive tests, and arrived at a clinical diagnosis using standard criteria for probable or possible AD.¹ Other diagnostic choices included multi-infarct de-

Table 1 Subject characteristics

Group	n	Age, y, mean (SD)	Sex, M/F	MMSE score, mean (SD)	Time from SPECT to death, mo, mean (SD)
Patients	70	77.1 (8)	35/35	13.2 (8.5)	29.3 (15)
Autopsied controls	14	80.4 (8)	9/5	27.9 (2.0)	22.9 (18.6)
Nonautopsied controls	71	73.3 (11)	28/43	28.8 (1.3)	NA

MMSE = Mini-Mental State Examination; NA = not applicable.

mentia, cerebrovascular disease without dementia, frontotemporal dementia, dementia with Lewy bodies, and Binswanger's syndrome. The clinical diagnostic evaluation was accompanied by a statement of the degree of certainty in the diagnosis, using a four-point scale. This individual was blinded to all imaging and neuropathologic results.

The same individual reviewed the neuropathologic report at a different time, blinded to all clinical and imaging data. The neuropathologic report included a description of the gross and microscopic histology and a pathologic diagnosis made by a senior neuropathologist. Although the pathologic diagnosis was thus usually obvious from the report, at times interpretation was required. The diagnostic options were AD, multi-infarct dementia, frontotemporal dementia, stroke, dementia with Lewy bodies, and Binswanger's syndrome. In addition, the rater could grade Alzheimer's pathology as present, but not diagnostic. All data were entered at the time of interpretation using a laptop computer that did not permit alterations after a case was recorded.

Digital data from the SPECT images were transferred to a single laboratory where they were uniformly formatted and processed (University of Texas Southwestern Medical Center, Dallas), and then forwarded to a separate laboratory (Bio Imaging Technologies, Trenton, NJ) where they were interpreted. The data were evaluated for compliance with the imaging protocol and technical adequacy. Images were presented on a video monitor in sagittal, coronal, and axial formats. Ratings were performed independently by three raters (H.M., M.D., and R.V.), each of whom was blind to all clinical and pathologic data and each of whom was experienced in the interpretation of clinical SPECT imaging. Individual scans were presented to each rater in a random order, and all interpretations were recorded directly into a computer that did not permit subsequent alteration of the entry. Coronal, sagittal, and transverse SPECT projection data were displayed at one time. Two high-resolution monitors were used for image display. The reader adjusted image brightness and contrast, magnification and panning, and cine display to personal satisfaction. Readers had the option of evaluating the images in black and white or standard color schemes.

During an initial training session on a separate set of images, readers reached consensus on how to interpret images and judge artifacts and positioning. Raters evaluated each image for a number of different features. First, each image was assessed for technical quality. Next, the images were read as normal or abnormal, and brain regions were independently rated as hyperperfused: normal, mildly, or moderately hypoperfused (a single category), or severely hypoperfused. These ratings were performed for each lobar region, cerebellum, and the subcortical structures in each hemisphere. The last stage of image interpre-

tation included a final diagnosis, for which the choices were AD, multi-infarct dementia, frontotemporal dementia, and ischemia or vascular disease. Multiple diagnoses were permitted. Criteria for the presence of AD were previously agreed on to include either bilateral or asymmetric temporal or parietal lobe hypoperfusion or both. Readers indicated their personal degree of confidence in the diagnosis on a four-point scale.

Statistical analysis. Two different methods were used to assess the utility of SPECT. The primary analysis of interest was the incremental diagnostic value of SPECT after taking clinical diagnosis into account. To do this, clinical diagnosis (obtained by review as described above) and SPECT diagnosis were entered into a multivariate logistic regression model to predict the presence or absence of Alzheimer pathology. Alzheimer pathology was considered present if the neuropathology assessment was "AD" but not present if Alzheimer's changes were graded as present but not diagnostic. SPECT scans were considered positive for AD if at least two reviewers identified AD as the principal diagnosis with a moderate to high confidence. Statistical significance of SPECT diagnosis was assessed using models that first control for the clinical diagnosis. Two separate models were evaluated, one using all subjects and another using only patients with dementia. In the first case, it was assumed that all controls, whether they had been autopsied or not, were free of Alzheimer pathology. This method of analysis permitted the determination of what pathology to expect for individual subjects with specific combinations of imaging and clinical diagnoses drawn from a specified population.

In addition to this logistic regression analysis, a separate analysis evaluated the diagnostic performance of SPECT. In this analysis, sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and positive likelihood ratio were calculated. This analysis, therefore, simply evaluated SPECT as a diagnostic test, so that a "positive SPECT scan" for AD was evaluated in relationship to the presence or absence of AD neuropathology. The identical evaluation was performed for clinical diagnosis, in which case the diagnosis of "probable AD" or "probable or possible AD" was considered as a positive test for AD. This method of analysis permits the comparison of different types of diagnostic tests (clinical or imaging) in different populations.

Analysis of variance and χ^2 tests were used to assess baseline differences between groups for continuous and categorical variables. Two-sided *p* values are reported.

Results. During the initial image evaluation and quality control process, three studies were deemed technically inadequate, leaving a total of 155 studies for analysis. Of these, 70 were in patients with dementia and 14 were in

Table 2 Pathologic diagnoses vs SPECT and clinical diagnoses in 70 demented patients and 85 controls

Diagnosis	Neuropathology assessment		
	AD absent	AD present	Total
Clinical			
AD Absent	96	3*	99
Probable or possible AD	13†	43	56
Total	109	46	155
SPECT			
AD absent	101	17‡	118
AD present	8§	29	37
Total	109	46	155

* Neuropathologic diagnoses for false negatives were AD + Huntington's, AD + ischemic/vascular disease, and AD only.

† Neuropathologic diagnoses for false positives were nonspecific changes/unknown (3), frontotemporal lobar degeneration (4), ischemia/vascular disease (2), PD (3), and progressive supranuclear palsy (1).

‡ Neuropathologic diagnoses for false negatives were AD (9), AD + cerebrovascular disease (5), AD + Lewy bodies (2), AD + PD (1).

§ Neuropathologic diagnoses for false positives were PD (4), frontotemporal lobar degeneration (2), cerebrovascular disease (1), and normal (1).

control subjects for whom autopsy was performed later. An additional 71 control subjects were studied with SPECT, but autopsy was not performed on them. Demographic characteristics of these subjects, including the time from SPECT imaging to death, are provided in table 1. No significant differences were seen between groups for sex and time from SPECT to death. Patients with dementia and autopsied control patients did not differ in age; however, living controls were younger on average than either of the other two groups ($p = 0.003$).

Of the 70 patients with dementia, 32 (46%) were clinically diagnosed as having probable AD and 24 (34%) were diagnosed as having possible AD. These diagnoses were established solely by review of the clinical information in the protocols. The remaining 14 patients (20%) were given clinical diagnoses of multi-infarct dementia (7), frontotemporal dementia (2), Lewy body (1), and other (4). None of the controls, either living or having had autopsy performed, were clinically diagnosed as having AD or any non-AD dementia. In contrast, 35 patients (50%) were diagnosed by SPECT imaging as showing evidence of AD. SPECT scans from two control subjects (one living and one autopsied) were interpreted as positive for AD.

Table 2 provides measures of true positive, true negative, false-positive, and false-negative findings for clinical diagnosis vs neuropathology and SPECT imaging versus neuropathology. The tables assume that control subjects without autopsies were truly negative for AD pathology. These tables also show the actual pathology when either diagnostic criterion produced a false-negative or false-positive finding. For both techniques, false-negative findings were often related to combined pathology, with AD plus an additional pathologic process. False-positive findings included a number of different pathologic conditions, including PD and frontotemporal dementia.

Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and positive likelihood ratios for clinical and SPECT diagnoses relative to pathology are provided in table 3.

The logistic regression model was fit using clinical diagnosis alone, SPECT diagnosis alone, and the combination of clinical and SPECT diagnoses. The reference groups used for these analyses were subjects who did not have clinical diagnoses of AD (when the clinical diagnosis model was evaluated), or who did not have SPECT diagnoses of AD (when the SPECT diagnosis model was evaluated). These models demonstrated that the clinical diagnosis of probable or possible AD is a highly significant predictor of Alzheimer pathology, increasing the odds of having AD over patients without these diagnoses 172 times for a diagnosis of probable AD and 64 times for possible AD. The SPECT image interpretation of AD alone is also a significant predictor of Alzheimer pathology, increasing the odds of having AD over subjects with a negative SPECT scan by a factor of 22. When SPECT and clinical diagnoses are considered together, a positive SPECT interpretation increases the odds of having AD by an additional factor of five (compared with those with a negative SPECT image), after taking into account any increase in odds associated with the clinical diagnosis. This incremental predictive value of SPECT is significant ($p = 0.018$).

These data are presented clinically in table 4. The clinical diagnosis of probable AD has an 84% likelihood of being associated with AD pathology. In the presence of a negative SPECT scan, this likelihood decreases to 70%, whereas a positive SPECT scan increases the likelihood to 92%. For the clinical diagnosis of possible AD, a similar result was obtained (67% without SPECT, 84% with a positive SPECT, and 52% with a negative SPECT). When this analysis was repeated excluding all control subjects, both the clinical diagnosis of AD, the SPECT diagnosis of AD, and the combined clinical and SPECT diagnoses remained significant predictors of neuropathologic AD.

Because varying delays occurred between SPECT imaging and autopsy, we also evaluated whether the time between the SPECT scan and death was a factor in determining the value of the scan. Positive and negative predictive values for SPECT vs autopsy in patients who died <1 year, between 1 and 2 years, 2 to 3 years, 3 to 4 years, or >4 years after SPECT scanning did not significantly differ.

Discussion. SPECT brain perfusion imaging has been widely reported to differentiate patients with AD from both control subjects and other dementing illnesses in a variety of studies.^{5,11-14} A recent review of the data on SPECT imaging in dementia by the American Academy of Neurology Therapeutics and Technology Assessment Subcommittee suggested that SPECT was an established technique for supporting the clinical diagnosis of AD.¹⁵ Dementia practice parameters¹⁶ list SPECT as an optional part of the dementia evaluation. Despite this enthusiasm, the data supporting the clinical utility of SPECT imaging have had several limitations. The first is that the use of clinical diagnoses as opposed to neuropathologic ones as the "gold standard" for SPECT imaging may be inaccurate. Secondly, the true utility

Table 3 Sensitivities, specificities predictive values, accuracy, and positive likelihood ratios for clinical- and SPECT-based diagnosis rules, based on different clinical populations

Population	Sensitivity/specificity	PPV/NPV	Accuracy	LR-Pos
Clinical diagnosis rule				
All subjects				
Probable AD	59/95	84/85	85	12.8
Possible or probable AD	93/88	77/97	90	7.8
SPECT	63/93	78/86	84	8.6
SPECT + probable AD	41/98	90/80	81	22.5
SPECT + possible or probable AD	61/96	88/85	86	16.6
SPECT or possible or probable AD	96/84	72/98	88	6.1
Autopsied subjects only				
Probable AD	59/87	84/63	71	4.5
Possible or probable AD	93/66	77/89	81	2.7
SPECT	63/82	81/65	71	3.4
SPECT + probable AD	41/95	90/57	65	7.8
SPECT + possible or probable AD	61/89	88/65	74	5.8
SPECT or possible or probable AD	96/58	73/92	79	2.3
Patients with dementia only				
Probable AD	60/80	84/53	67	3.0
Possible or probable AD	96/48	77/86	79	1.8
SPECT	64/76	83/54	69	2.7
SPECT + probable AD	42/92	90/47	60	5.3
SPECT + possible or probable AD	62/84	88/55	70	3.9
SPECT or possible or probable AD	98/40	75/91	77	1.6

Sensitivity: true positives/(true positives + false negatives); specificity: true negatives/(true negatives + false positives); PPV: true positives/(true positives + false positives); NPV: true negatives/(true negatives + false negatives); accuracy: (true positives + true negatives)/total; LR-pos: sensitivity/(1-specificity).

PPV = positive predictive value; NPV = negative predictive value; LR-Pos = positive likelihood ratio.

of a test is best evaluated by defining the additional information contributed by the test over and above that obtained in the standard clinical evaluation. When the clinical evaluation is used as the final determination of validity, this is impossible. Finally, another frequent shortcoming of many reports is that the most typical cases of AD are chosen for study, and very clear-cut comparison diagnoses (e.g., normal older subjects) are chosen as controls. Although this improves confidence in the clinical standard of validation, it limits the utility of the results. For example, differentiation of typical AD from healthy older individuals is usually not a clinically useful finding.

This report eliminates many of the shortcomings of prior studies. The use of neuropathologic diagnoses provides the highest standard of validation for a study of this sort. The sample of subjects includes patients with a variety of dementias, and, although not necessarily typical of a general practice, does reflect a broad spectrum of cognitive disorders likely to be referred for a specialized evaluation. Most importantly, the experimental procedure permitted the separate evaluation of clinical and SPECT diagnostic

accuracy, allowing the determination of the additional value of SPECT imaging over accuracy of clinical diagnosis.

In this study, the case record reviews resulted in clinical diagnoses that were highly predictive of the presence of AD on pathology. This is consistent with previous reports that clinical criteria are reasonably valid.¹⁷ Clear differences were seen in sensitivity and specificity, depending on whether probable or possible AD was diagnosed, with the inclusion of possible AD raising sensitivity but lowering specificity. Not surprisingly, when only patients with dementia were included, clinical diagnoses were far less specific but not less sensitive, because no control subjects were falsely diagnosed as demented. For the same reason, a similar picture emerged for SPECT diagnoses, with reduction in specificity when only subjects with dementia were evaluated. Interestingly, the sensitivity, specificity, and predictive values of SPECT alone were generally comparable to the clinical diagnosis of probable AD. The addition of possible AD cases clearly increased the sensitivity of clinical diagnoses. However, as has been shown in other autopsy studies² this increase in sensitivity when possible AD

Table 4 Results of logistic regression models showing the fraction of all subjects who actually have Alzheimer neuropathologic findings for three levels of clinical diagnosis (AD absent, possible AD, and probable AD) without SPECT, with a negative SPECT scan, and with a positive SPECT scan

Subjects	Clinical diagnosis		
	AD absent	Possible AD	Probable AD
All			
If SPECT not done	0.03	0.67	0.84
SPECT negative for AD	0.02	0.52	0.70
SPECT positive for AD	0.11	0.84	0.92
Demented patients only			
If SPECT not done	0.14	0.67	0.84
SPECT negative for AD	0.10	0.54	0.72
SPECT positive for AD	0.30	0.82	0.91

Results are presented for all subjects (70 demented patients and 85 controls) and for dementia patients only.

cases are included comes at the price of reduced specificity, which is considerable when only the dementia group is included. Finally, it is worth noting that the addition of SPECT imaging to clinical diagnosis resulted in lower overall accuracy than the use of either technique alone. This is because the requirement of both a positive clinical diagnosis and a positive SPECT diagnosis is more stringent than requiring only one positive test, resulting in lower sensitivity. However, requiring two positive diagnostic tests increases specificity so that the positive likelihood ratio increases. The positive likelihood ratio is a useful clinical metric because it provides an index of the incremental value of a test by defining the post-test probability for a given pretest probability. Positive likelihood ratios greater than 10 generate large, usually clinically relevant changes in probability of a diagnosis; values between 5 and 10 generate modest changes in probability; and values below 5 generate relatively small but sometimes useful changes.¹⁸ For these data likelihood ratios depended to a considerable extent on the population sampled, with relatively small to modest effects seen when only patients with dementia were evaluated.

In the clinical situation where diagnoses have imperfect predictive power, SPECT can play a role. Thus, even with the high likelihood of pathologic AD conferred by a clinical diagnosis of probable AD, SPECT significantly improves diagnostic accuracy, with the likelihood of AD pathology increasing by 7 to 8% to a value above 90% if the SPECT scan is positive. The increased probability of AD is twice as great if a SPECT scan is positive when the clinical diagnosis is possible AD. That is, a clinical diagnosis of possible AD with a positive SPECT scan is as likely to be associated with AD pathology as a clinical diagnosis of probable AD alone. These results thus indicate a demonstrable incremental value in

both a positive and negative SPECT scan in addition to the clinical diagnosis, and that this incremental value is greater in atypical or uncertain cases.

Another study evaluated the ability of SPECT to predict histopathology in dementia, finding a sensitivity of 86, specificity of 73, positive predictive value of 92, and negative predictive value of 57 for a study of 54 patients with dementia and no controls.¹⁹ These figures are comparable to our results in the dementia-only analysis, although the sensitivity we report is lower. The lower sensitivity could reflect the fact that we did not exclude cases with extensive cerebrovascular disease, and mixed dementia produced a substantial number of false-negative findings in our report. Two other SPECT studies have shown very high correspondence between imaging and pathologic diagnoses,^{20,21} but these studies have involved relatively small numbers of highly selected patients.

Although these data clearly demonstrate general clinical utility of SPECT imaging in dementia, a number of questions about the specific situations in which SPECT imaging may be useful remain unanswered. The subjects in this report were moderately to severely demented, as evidenced by a mean Mini-Mental State Examination score of 13. Whether SPECT would have greater or lesser utility in less severe cases is unknown. The degree of clinical uncertainty in the diagnosis might also be expected to influence the clinical utility of SPECT. Although we did not find that SPECT was more useful in situations in which the clinical certainty was low (perhaps because clinical certainty did not relate to the accuracy of the diagnosis), our sample size was small for this analysis. Similarly, specific differential diagnoses might be presumed to be more or less useful. A number of reports have suggested that SPECT is most useful in differentiating AD from frontotemporal dementias^{14,22,23} and least useful in differentiating AD from PD and vascular dementia.^{5,24} However, the sample of non-Alzheimer dementias was inadequate to evaluate the utility of specific differential diagnoses. Finally, the utility of SPECT in comparison to other diagnostic tests was not evaluated. For example, previous studies have shown that both CT and MRI may provide useful diagnostic information in the evaluation of patients with dementia.^{25,26} It is not clear how SPECT performs in relation to clinical diagnosis when CT and MRI are included in the evaluation process.

The correct diagnosis of the cause of dementia is increasingly recognized as important because of better understanding of genetic risks and disease mechanisms. Some potential therapeutic options (e.g., anti-amyloid agents, vaccination, or neural transplantation) might be associated with high risks, necessitating accurate diagnoses. The addition of SPECT in this situation could increase the likelihood of a correct diagnosis. Furthermore, the availability of treatment for AD has shifted the strategy for the diagnosis of AD from a traditional approach of ex-

cluding a host of diseases, to an approach that seeks typical signs and symptoms with confirmatory tests done to support a positive diagnosis in some situations. SPECT perfusion imaging is clearly a technique that may provide other valuable information in addition to the clinical diagnosis.

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