Evaluating Early Dementia With and Without Assessment of Regional Cerebral Metabolism by PET: A Comparison of Predicted Costs and Benefits

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Evaluating dementia in patients with early symptoms of cognitive decline is clinically challenging. Growing evidence indicates that appropriate incorporation of PET into the clinical work-up can improve diagnostic and prognostic accuracy with respect to Alzheimer's disease (AD), the most common cause of dementia in the geriatric population. The precise diagnostic role of PET and its economic impact in this context, however, have not been systematically examined previously. **Methods:** We compared the relative value of 2 strategies for assessing whether early AD is responsible for cognitive symptoms in geriatric patients: (a) a conventional approach, based largely on establishing clinical criteria for the presence of dementia and excluding non-AD etiologies that could contribute to the patient's symptoms, and (b) a proposed approach using PET to examine regional cerebral metabolism and look for characteristic patterns of abnormal metabolism. The total costs (measured in dollars) and benefits (measured in number of accurate diagnoses) of diagnostic testing and clinical outcomes accruing to each strategy were calculated using formalized tools of decision analysis. The primary outcome measure by which the strategies were compared was the ratio of costs to benefits obtained following each approach. **Results:** Following the proposed approach led to improved accuracy in identifying early AD, without adding to the overall costs of diagnosis and treatment ($3,433 vs. $3,564 per patient approached by the proposed or conventional algorithm, respectively). The strategy making use of PET was associated with a reduced rate of false-negative and false-positive findings compared with the conventional approach (3.1% vs. 8.2% and 12.0% vs. 23.0%, respectively, at a prevalence of 51.6% in the studied symptomatic population) and a cost savings of $1,138 per correct diagnosis rendered ($4,047 vs. $5,185). The lower cost per unit benefit for the proposed strategy was maintained over a wide range of tested values for variables of sensitivity, specificity, costs of PET and long-term care, and varying approaches to the use of structural neuroimaging. **Conclusion:** Appropriate use of PET for evaluating early dementia in geriatric patients can add valuable information to the clinical work-up, without adding to the overall costs of evaluation and management, resulting in a greater number of patients being accurately diagnosed for the same level of financial expenditure. Thus, the opportunity exists for diminishing the morbidity of dementia economically, with earlier institution of more appropriate management in evaluated patients.

Key Words: Alzheimer's disease; dementia; PET; FDG; functional brain imaging; cost-to-benefit ratio; cost-effectiveness; decision tree; decision analysis

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Dementia exacts a huge toll on our health and welfare and, as mean life expectancy continues to rise, the magnitude of this problem is growing. It is estimated that 8% of people who are ≥65 y old suffer from the most common form of dementia, Alzheimer's disease (AD) (1,2). Disease prevalence climbs rapidly with age, and at least 30% of people who are ≥85 y old are afflicted with AD (3,4). An even larger number of caregivers and family members must cope with the emotional and practical burden of the disease's relentless and irreversible decline in cognition, functioning, and behavior. The disease also has enormous finan-

cial consequences on families and the larger society. In the United States alone, >$90 billion will be spent on AD-related expenses each year (5,6).

Dementia is generally defined by documented decline in multiple cognitive functions (e.g., memory, language, visuospatial ability), sufficiently severe to interfere with daily life in an alert patient (1). AD is a dementia syndrome that progresses insidiously, eventually altering memory, higher intellectual function, language, praxis, and visuospatial and other cognitive abilities. A definite diagnosis of AD can be made only by histopathologic examination of brain tissue, which rarely occurs before the patient's death (7). The identification and differential diagnosis of dementia are especially challenging in its early stages, partly because of the difficulty in distinguishing it from the mild decline in memory that can occur with normal aging and from mild cognitive manifestations of other neuropsychiatric conditions, such as depression. Systematic studies indicate that the frequency of unrecognized memory impairment or dementia could range from 50% to 90% of cases (8,9). Physicians frequently err by failing to make the diagnosis of AD when the disease is present and by diagnosing early AD when it is in fact absent (8–13). Given the large number of their older patients likely to become affected, physicians require more accurate and effective methods to work through the differential diagnosis of early symptoms of cognitive impairment.

This need for accurate diagnoses has become even more important now that several prescription medications for the treatment of mild to moderate AD are available. Controlled clinical trials have shown that cholinesterase inhibitors can improve, or delay decline in, memory and other cognitive functions in AD patients (14–20). These treatments can cut by more than half the proportion of patients requiring nursing home placement over a given period of time (21,22). Cholinergic (and other (23)) agents also have beneficial effects with respect to reducing behavioral problems, improving patients' functional abilities, and decreasing caregiver burden (16,24–27). Those studies that have examined the long-term effects of cholinesterase inhibitors indicate that drug treatment produces an average delay in cognitive decline in AD patients of 9–12 mo, relative to the time course of untreated patients (26,28,29), and a delay in the need for institutionalization of 18 mo on average (30). This may represent a substantial portion of the patients' remaining life expectancy. Moreover, delaying the institution of therapy by as little as 6 mo—in addition to carrying the inherent adverse consequence of depriving the patient of the short-term advantages of potentially enhanced mental activity and diminished cognitive decline during that time—may have long-term disadvantages as well (16,26,31). In a randomized, placebo-controlled trial of the cholinesterase inhibitor galantamine in patients with mild to moderate AD, Raskind et al. (16) found that the drug significantly improved cognitive function relative to the placebo after 6 mo of treatment; during an ensuing 6-mo open-label treatment period, the patients who were originally in the placebo group were also given active drug. At 1 y, better cognitive performance was seen in patients who began drug treatment from the beginning of the trial than in those who had been delayed with the placebo for 6 mo. Similar detrimental effects have also resulted from delaying the institution of therapy with either rivastigmine (19) or donepezil (31). Thus, the need is apparent for accurate and early diagnosis of AD.

Along with the advantages of allowing earlier institution of pharmacotherapy, early detection of AD offers several additional benefits. For example, many people may want to know about a poor prognosis while their memory losses are relatively mild to better plan for their future. This knowledge allows physicians, patients, and family members the opportunity to address safety issues as well as to identify surrogate decision makers and sources of caregiver support early in the disease process. Furthermore, such benefits have been shown to reduce the need for nursing home placement of patients with mild dementia by 82%, to delay nursing home placement of all AD patients by an average of 11 mo, and to generally enhance quality of life for patients and their families (32). Finally, early accurate diagnostic approaches may also help to avoid the costs, efforts, and frustrations associated with years of multiple diagnostic evaluations. As summarized by the U.S. Agency for Health Care Policy and Research in 1996, "early recognition of the condition has important benefits," and yet, "early-stage dementia is often unrecognized or misdiagnosed" (33).

A noninvasive neurobiologically based approach through molecular imaging with PET could be of great use in addressing this diagnostic challenge. Mounting evidence indicates that the dementing process of AD begins years before the clinician can confirm the diagnosis using conventional approaches to assessment (34,35) and that the associated cerebral changes can be detected by PET during these early stages of AD, and even preclinically (36,37). In a recent report by the members of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) (38), it was concluded that "PET scanning appears to have promise for use as an adjunct to clinical diagnosis [of AD]" on the basis of their review of published studies that showed diagnostic accuracies of 86%–100% for PET with ^{18}F-FDG, but they stopped short of directly endorsing PET in this context. Given that patients have the most to gain from effective therapeutic approaches that intervene as early as possible in the course of dementing illness—and that, on the one hand, conventional methods for evaluating those patients are inadequate for making reliable diagnostic and prognostic assessments in the early stages of their disease, whereas, on the other hand, PET can detect such disease even at the time of its earliest symptomatic expression—the question arises as to what is the most appropriate role for PET in the diagnostic process. On the basis of our own review and synthesis of the data available with which to address that question, we believe that PET is underused

for this purpose and have proposed applying it in a way that is more consonant with those data (39–43). In this study, we use formalized tools of decision analysis to compare the conventional approach, as guided especially by AAN reviews and recommendations, with an approach that attempts to take greater advantage of the direct cerebrometabolic information that imaging with PET can add to the diagnostic work-up of early dementia. We identify the sensitivity, specificity, and overall accuracy of each approach and assess the financial consequences of missed diagnoses. As our primary outcome measure, we compare the ratio of costs (measured in Medicare dollars) to benefits (measured in number of accurate diagnoses) accruing to each approach.

MATERIALS AND METHODS

Decision-Tree Analysis

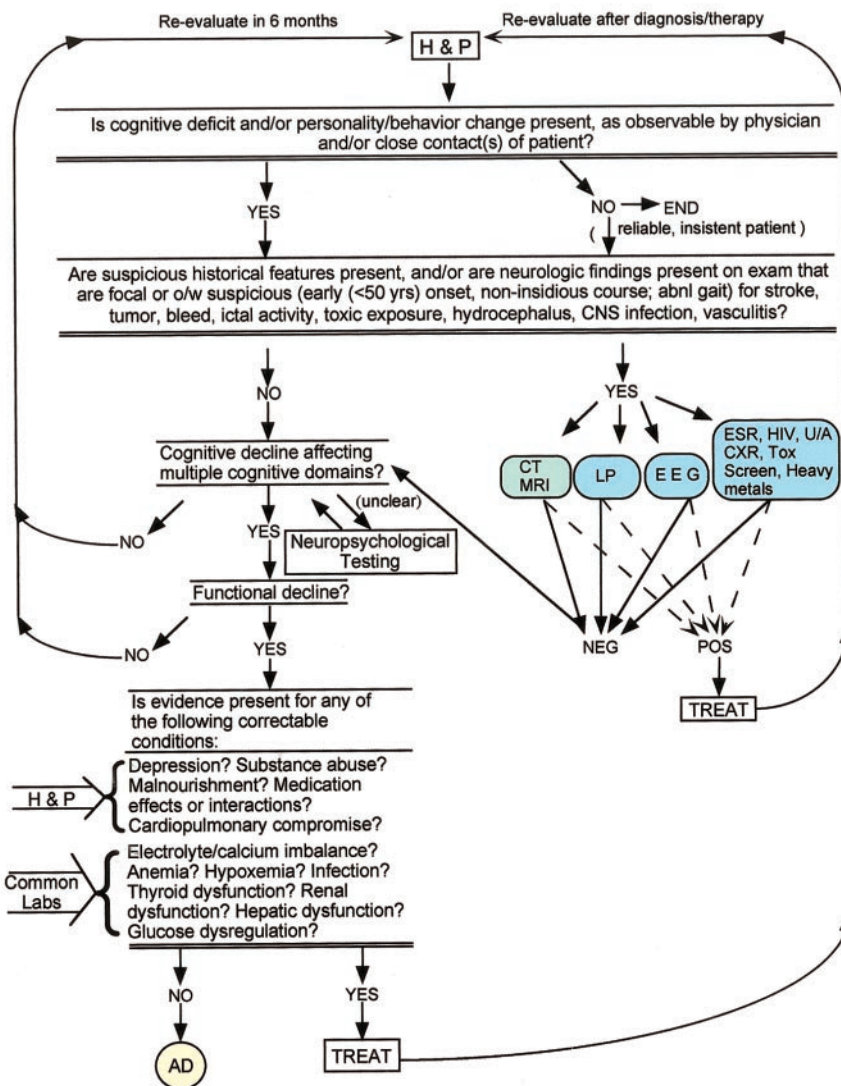The main endpoint measures (overall costs, number of accurate diagnoses, and cost per accurate diagnosis) were quantified from a payor perspective through established methods of decision analysis (44–47). This analysis involved 4 major components.

First, a decision-tree model was constructed to represent and compare 2 competing strategies: an algorithm reflecting current practice standards for expert evaluation of dementia (conventional algorithm) and the algorithm that we propose for evaluation of dementia (proposed algorithm). Dollar costs for medical care were assigned to each test and to each clinical outcome detailed in the model, as described below. The explicit probabilities for each of the branches in the decision tree were obtained as functions of explicitly defined variables (Table 1). The probabilities were computed using standard Bayesian analytic methods (46) where applicable. Essentially, diagnoses of AD were made with the conventional algorithm (Fig. 1) by documenting the presence of clinical criteria for dementia, followed by a deductive process of ruling out, or identifying and treating, other potentially confounding conditions (e.g., structural brain lesions, thyroid disease, depression). This represents the set of procedures recommended by the AAN (38,56) (and, in somewhat less comprehensively articulated fashion, by the American Association of Geriatric Psychiatry,

TABLE 1
Explicitly Modeled Variables of Decision-Tree Analysis

Algorithm	Variable	Value of variable in base-case analysis	Supporting literature or other justification
C, P	Prob. of initial comprehensive H&P (including neurologic examination)	1.00	Required part of evaluation
C, P	Prob. of needing CT or MRI	0.625, 1.00 initial evaluation (0.10 in comprehensive follow-up evaluation)	Set to be equal in both algorithms
C, P	Prob. of needing special tests or outside consultation (blue-shaded boxes in Figs. 1 and 2)	0.035 (initial evaluation only)	Refs. (48,49); set to be equal in both algorithms
C	Prob. of obtaining neuropsychologic testing	0.59	Ref. (50)
C	Prob. of having multiple cognitive domains affected (including patients undergoing neuropsychologic testing)	0.67 initial evaluation	Based on number of clinical dementias per documented AD case in Ref. (10) and adjusting AD prevalence to rate in Ref. (50)
		Additional 0.01 of remaining patients per month on follow-up evaluation	Based on conversion rates as documented in Refs. (51,52)
C	Prob. of functional decline (among those with multiple cognitive domains affected)	0.90	Estimate based on clinical experience (no published values found)
C, P	Prob. of potentially reversible cause of dementia evident on H&P or common laboratory tests	0.22	Refs. (48,49,53,54)
C, P	Prob. of identifying potentially reversible dementia by H&P or common laboratory tests and completely reversing it with therapy	0.045	Refs. (48,49,53,55)
C, P	Prob. of identifying potentially reversible dementia by CT or MRI, not found by H&P or common laboratory tests, and completely reversing it with therapy	0.00	Ref. (53)

C = conventional; P = proposed; Prob. = probability; H&P = history and physical examination; Ref. = reference.

FIGURE 1. Conventional algorithm used for diagnosis of AD. H & P = history and physical examination; exam = examination; o/w = otherwise; abnl = abnormal; bleed = bleeding; CNS = central nervous system; LP = lumbar puncture; E E G = electroencephalogram; ESR = erythrocyte sedimentation rate; U/A = urinalysis; CXR = chest x-ray; Tox = toxicology; NEG = negative; POS = positive; Labs = laboratory tests.

Alzheimer's Association, and American Geriatrics Society (*1*) as well as the American Medical Association (*57*)).

In comparison, the proposed algorithm used FDG PET in the diagnostic work-up of patients with early cognitive symptoms when appropriate, as defined by explicitly formulated criteria (Fig. 2); diagnosis of AD depended on identification of a characteristic pattern of regional cerebral metabolism on PET scans. Note that Figure 2 is not intended to indicate all tests that can or should be done to fully evaluate all patients with cognitive impairment but, rather, represents the steps in the decision pathway that we used to determine whether a PET scan was obtained on patients presenting with symptoms that could represent the early manifestations of AD or related diseases. In particular, between 1994 and 2001, the position of the AAN shifted from recommending that CT or MRI studies should be ordered only for patients with a specific indication identified by history or examination (*56*) to recommending that they be ordered for essentially all patients undergoing initial evaluation for dementia (*38*). This shift occurred largely because of intervening empiric documentation (*50*) showing that clinically important conditions were sometimes found on CT or MRI in patients who did not have any of the previously recommended

criteria for undergoing neuroimaging. Figure 2 should not be interpreted as being in support of the former position (*56*); it illustrates only those steps necessary for the evaluating physician to take before deciding whether to order FDG PET. Accordingly, in this analysis, we compared the conventional algorithm and the proposed algorithm with the frequency of structural neuroimaging set at levels determined by each set of AAN guidelines, and the comparison was always made in a balanced manner. For example, when MRI scans were obtained for 100% of patients in the conventional algorithm, they were also obtained for 100% of patients in the proposed algorithm with which it was being compared, and the associated costs comparably accrued to both algorithms.

Second, the medical literature was reviewed to determine reliable means and ranges for all modeled variables; these were specifically oriented, wherever time-stratified or severity-stratified data were available, toward evaluation of patients with clinical presentations indicating an early stage of cognitive decline. To minimize the chance of introducing any bias operating against the algorithm emulating AAN recommendations (Fig. 1) (*50,55,56*), we implemented the following policy: Whenever the values of
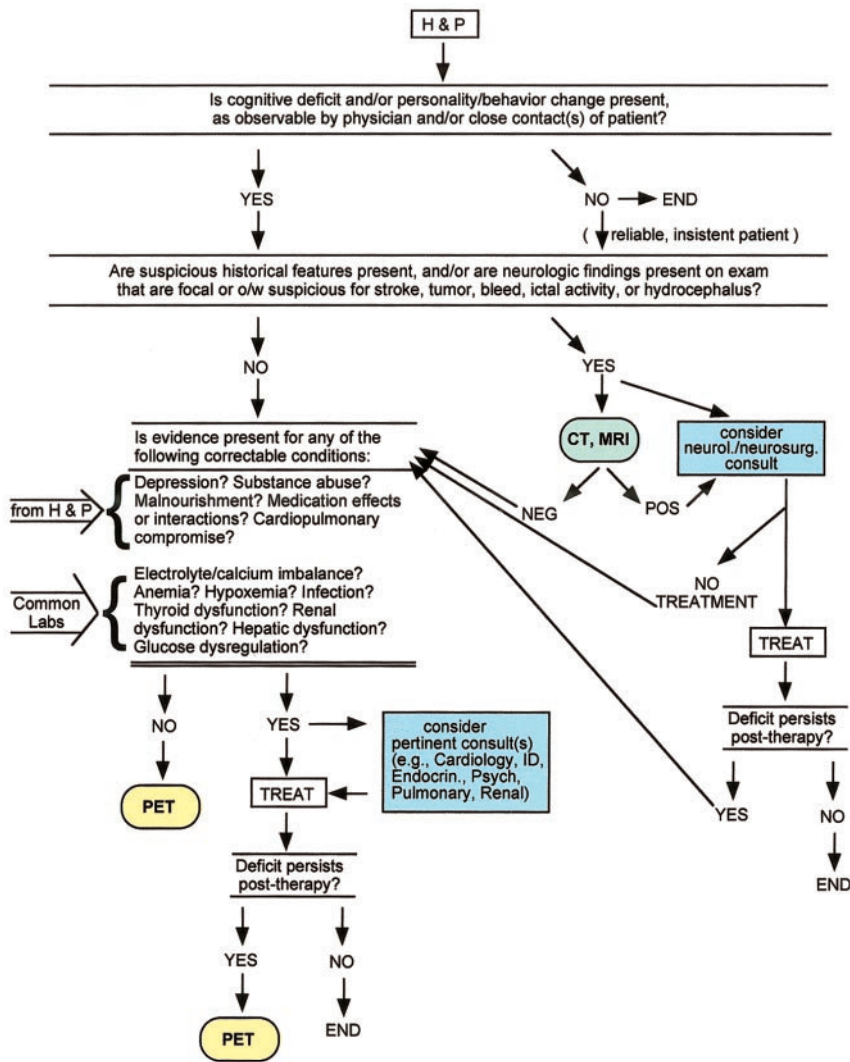
FIGURE 2. Proposed guidelines for determining when to obtain brain PET study in evaluation of geriatric patients with early symptoms of cognitive decline. H & P = history and physical examination; exam = examination; o/w = otherwise; bleed = bleeding; neurol. = neurologic; neurosurg. = neurosurgical; consult = consultation; NEG = negative; POS = positive; Labs = laboratory tests; ID = infectious disease; Endocrin. = endocrinology; Psych = psychology.

outcome-probability variables were ascertainable from the data presented in the AAN's own published practice parameter papers (*38,51,56*), or in the background paper for, or systematic study of, AAN parameters (*50,55*), those values were used for the decision analysis model. To obtain all other values, MEDLINE (MEDLARS On-Line) and BIOSIS (BioScience Information Service) databases were used to search for research articles published between 1985 and 2000. The results of the search were limited to human-related articles published in English. The search was conducted using the keyword "dementia," cross-referenced with 1 or more of the following other relevant terms: early diagnosis, early evaluation, Alzheimer or Alzheimer's, cognitive impairment, cognitive dysfunction, practice parameter, laboratory, delirium, depression, neuropsychological testing, CT, MRI, PET, sensitivity, specificity, follow-up, and reversible. Articles were required to include at least some patients who were geriatric (≥60 y old) and who had mild dementia (Mini-Mental State Examination scores of ≥20). Articles were excluded if they involved diagnostic work-ups lacking the majority of types of examinations used in the context of either the conventional or the proposed algorithm.

Values for all variables were tabulated along with the supporting literature sources (Tables 1–3) and were entered into the model

at the appropriate branch points of the decision tree. The prevalence of AD in the study population used in the analysis was determined by applying the average diagnostic sensitivity and specificity values cited by the AAN in their most recent review of those data (*38*) to the distribution of final diagnoses resulting empirically from systematic application of the conventional algorithm (*50*), giving a calculated prevalence of 51.6% of patients studied. This estimate not only had the advantage of being derived from a realistic empiric situation but also accorded well with the theoretic principle that the most generally informative test of a diagnostic algorithm usually occurs when it is applied to patients from a population who, before diagnosis, are thought to possess an approximately equal chance of having or not having the disease of interest.

Cost values were defined using current Medicare reimbursement rates for all variables where those had been established and by explicitly stated methods and literature sources otherwise (Table 4). In particular, because Medicare reimbursement rates for PET with FDG were established for whole-body studies but not (at the time of our investigation) for dedicated brain studies, we calculated a Medicare-consistent cost for brain PET by multiplying the Medicare whole-body reimbursement rate by a factor (0.70)

TABLE 2
Sensitivity and Specificity of PET Compared with Neuropathologic Confirmation of Presence or Absence of AD

No. of patients	Major findings	Comments	Ref.
13 AD, 7 Non-AD	Sens = 92%, Spec = 71%	Pooled analysis across 3 studies (*58–60*) providing small groups of pathologically confirmed cases	(*39*)
16 AD, 6 Non-AD	AD identified in 13/14 (Sens = 93%) of AD-only and 1/2 AD-positive cases (overall Sens = 88%). Absence of AD confirmed in 4/6 cases (Spec = 67%)	Single-institution series of 22 pathologically confirmed cases; 14 patients had AD as only pathologic diagnosis, 1 had AD-positive Lewy bodies, 1 had AD-positive PSP	(*61*)
97 AD, 41 Non-AD	Sens = 94%, Spec = 73%. For subset of 55 patients with documented early (questionable or mild) dementia, Sens = 95% and Spec = 71%	Data represent current status of FIND-AD investigation, reported in Ref. (*43*)	(*43*)

Ref. = reference; AD = cognitively impaired secondary to AD; Non-AD = no AD identified on neuropathologic examination; Sens = sensitivity with respect to correctly identifying presence of AD; Spec = specificity with respect to correctly specifying that AD is absent; PSP = progressive supranuclear palsy; FIND-AD = FDG-PET International Nexus for Diagnosis of Alzheimer's and Other Dementias.

reflecting the ratio of reimbursement rates from private insurance companies that compensate our institution for dedicated brain and whole-body studies. This led to a brain PET cost of $1,661 for our base-case analysis (which is also similar to what our institution actually charges for those studies). No time-based cost discounting (*47*) was incorporated into the decision-tree model because all evaluations were assumed to be completed within 6 mo from the time of patients' initial presentation.

Third, overall cost for each strategy was calculated by summing the products of the branch-probability and cost values for every branch of each strategy. The expected number of accurate diagnoses for each strategy was calculated by determination and summation of path probabilities to all AD outcomes, coupled with sensitivity and specificity values obtained from reviewing the most pertinent literature, as detailed below. The blue-shaded portions of the algorithms indicate the role of specialized tests and consultations in dementia evaluations. Note that they were included in the diagrams for the sake of conceptual completeness but, as evident from our cost tabulations (Table 4), we only explicitly modeled the costs of their structural neuroimaging component. We did so because our review of the literature indicated that the frequency for needing other kinds of specialized evaluation in the context of dementia work-up was low, and their contribution toward establishing the final diagnosis was even lower. Thus, they would not be expected to impact significantly on our outcome measures (particularly because overall they would be used similarly in conventional and proposed algorithms). Calculations of cost savings between the competing strategies were determined by subtracting the expected cost per accurate diagnosis for the proposed algorithm from the expected cost per accurate diagnosis for the conventional algorithm (i.e., a higher overall cost per unit benefit for the proposed algorithm would yield a negative cost savings). This cost-savings method of comparing the costs per unit benefit accruing to each strategy was used in preference to the method of incremental computation of the summary measure (*47*) because of the presence of significant structural differences in the 2 strategies being analyzed rather than PET being used as a simple add-on test.

TABLE 3
Sensitivity and Specificity of Conventional Clinical Evaluation Compared with Neuropathologic Confirmation of Presence or Absence of AD

No. of patients	Major findings	Comments	Ref.
94 AD, 40 Non-AD	Sens = 83%, Spec = 55% Prob AD Sens = 85%, Spec = 50% Prob AD + Poss AD	Patients with new onset (<1 y) of symptoms of dementia when first seen; diagnoses based on average follow-up of 3.0 y	(*10*)
80 AD, 24 Non-AD	Sens = 49%, Spec = 100% Prob AD Sens = 96%, Spec = 61% Prob AD + Poss AD	40% of patients lived in long-term care facilities. Diagnoses based on annual assessments from time of referral until death. Followed for average of 2.3 y, at which time majority of patients were moderately or severely demented	(*63*)
68 AD, 12 Non-AD	Sens = 50%, Spec = 70% Prob AD	Diagnoses based on annual assessments from time of referral until death	(*64*)

Ref. = reference; AD = cognitively impaired secondary to AD; Non-AD = no AD identified on neuropathologic examination; Sens = sensitivity with respect to correctly identifying presence of AD; Spec = specificity with respect to correctly specifying that AD is absent; Prob AD = diagnosis of probable AD by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria; Poss AD = diagnosis of possible AD by NINCDS–ADRDA criteria.

TABLE 4
Costs Accrued to Conventional (C) and Proposed (P) Algorithms

Algorithm	Item	Cost of item in base-case analysis	Medicare rate or other cost basis
C, P	H&P		
	Initial comprehensive	$149.47	Medicare
C	Follow-up (used to reassess for dementia in previously nondemented patient)	$62.33	Medicare
C, P	Focused follow-up (used after treatment of abnormality found on H&P or laboratory tests)	$38.36	Medicare
C, P	MRI		Medicare
	Without contrast	$608.12	
	With and without contrast	$1,294.17	
C	Neuropsychologic testing	$84.33	Medicare
C, P	Laboratory tests		Medicare
	CBC	$4.76	
	ESR	$3.73	
	T_4	$8.95	
	TSH	$23.21	
	Basic metabolic panel	$11.70	
	Hepatic panel	$11.29	
	Folate (RBC, serum)	$44.25	
	Vitamin B_{12} level	$20.83	
	Syphilis serology	$11.40	
P	Brain PET	$1,661	Medicare × private insurance ratio, brain to whole body
C, P	Extra care needed for AD patient who progresses past early stage while going untreated because of false-negative diagnosis	$30,000	$40,000/y of care (51) × 0.75-y (minimum) average delay of progression with therapy (16,19,26,28–31)
C, P	1-y supply of cholinesterase inhibitor unnecessarily prescribed to Non-AD patient because of false-positive diagnosis	$1,500	Median cost for donepezil and rivastigmine (most common inhibitors in current use) based on survey of local pharmacies

H&P = history and physical examination; CBC = complete blood count; ESR = erythrocyte sedimentation rate; T_4 = thyroxine (L-3,5,3′,5′-tetraiodothyronine); TSH = thyroid-stimulating hormone; RBC = red blood cell; Ref. = reference; Non-AD = no AD identified on neuropathologic examination.

Costs were based on Medicare outpatient reimbursement rates whenever possible. Costs include professional and technical components, where applicable, as listed in the 2001 Medicare Fee Schedule booklet.

Finally, because the values of some branch probabilities and costs vary across clinical settings, range-of-variable analyses were performed on the most potentially variable and critical values (i.e., cost, sensitivity, and specificity of PET studies and cost of AD care). Specifically, this involved evaluating, over a specified range of each variable, the associated range of expected cost savings. A commercially available software product, Data 3.0 for PowerMac (TreeAge Software, Inc., Williamstown, MA), was used to construct the decision tree and to assist in the calculations underlying the analyses. Except as explicitly explained above, the methods used in this investigation were in compliance with the methodologic principles of economic analysis that we outlined previously (47).

Sensitivity and Specificity of PET

Hundreds of patients with clinically diagnosed, and in some cases histopathologically confirmed, AD from many independent laboratories have been studied using PET measures of cerebral blood flow, glucose metabolism, or oxygen utilization. The resulting findings have been the subject of several recent reviews (39,65–67), and the principal findings that have emerged from that experience are as follows. A consistent pattern of focally decreased cerebral metabolism occurring in AD patients has been identified with PET; the hypometabolism involves neocortical association areas (especially parietotemporal cortex), but largely spares basal ganglia, thalamus, cerebellum, brain stem, and the cortical regions mediating primary sensory and motor functions. The extent of hypometabolism is correlated with the severity of cognitive impairment (65) and often shows right–left hemispheric asymmetry (68), particularly in the earlier stages of disease. Right-handed patients with primarily visuospatial symptoms show predominantly right-sided hypometabolism, whereas those with language deficits are more likely to show left-sided hypometabolism, with both kinds of cases becoming more symmetric as disease progresses.

Studies comparing neuropathologic examination with PET imaging are the most informative in assessing diagnostic value (Table 2). In a pooled analysis (39) of 3 previously published studies (58–60), histopathologically confirmed sensitivity and specificity of PET for detecting the presence of AD were 92% and 71%, respectively. In the largest single-institution series, Hoffman et al.

(61) found sensitivity and specificity of PET for AD to fall in the ranges of 88%–93% and 63%–67%, respectively. A multicenter study, FDG-PET International Nexus for Diagnosis of Alzheimer's and Other Dementias (FIND-AD), was recently organized to compare dementia diagnosis using FDG PET with neuropathologic diagnosis (43). The investigators collected data from an international consortium of clinical facilities that had acquired brain FDG PET and histopathologic data for patients undergoing evaluation for dementia. The PET results identified patients with AD with sensitivity and specificity of 94% and 73%, respectively. Because this latter study included >3 times as many patients as the 4 previous studies combined, the present base-case analysis used the AD sensitivity and specificity values determined for PET in the latter study. These values also accorded with the ranges reported in a broader review of the PET literature (62) that included studies lacking neuropathologic confirmation of diagnoses and that reported sensitivities ranging from 90% to 96% and specificities ranging from 67% to 97%. Our investigation included range-of-variable analyses exploring the full ranges of sensitivity and specificity values identified across all of these studies.

Sensitivity and Specificity of Clinical Evaluation

In the recent report of the Quality Standards Subcommittee of the AAN (38), an organization that has been the source of arguably the most comprehensive and authoritative guidelines and standards for the clinical evaluation of dementia in the last several years, 3 class I studies (10,63,64) were identified in which the diagnostic value of conventional clinical assessment could be meaningfully measured (Table 3). (Class I indicates "a well designed prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, and enabling the assessment of appropriate tests of diagnostic accuracy.") Only 1 of those studies (10) focused on evaluating dementia at a relatively early stage. To be included in that study, patients were required to have had onset of dementia symptoms within 1 y of entry. All of the 134 patients evaluated underwent a complete standardized diagnostic work-up comprised of a comprehensive medical history and physical examination, neurologic examination, neuropsychologic testing, laboratory tests, and structural neuroimaging, and an average of 3 additional years of clinical follow-up. Sensitivity of this assessment for AD was 83%–85%, whereas specificity was 50%–55%. It should be emphasized that this was not the diagnostic accuracy of initial clinical evaluation but of an entire series of evaluations repeated over a period of years (in contrast to the accuracies estimated for PET, based on testing performed once and at an early stage of disease). Nevertheless, a conservative bias (i.e., in favor of the conventional algorithm) was permitted in the present analysis, by exercising the assumption that these levels of accuracy (with sensitivity and specificity taken at their mean values of 84% and 52.5%, respectively) could be achieved in only

6 mo of total evaluation time, to allow a match with the maximal length of time required for diagnoses to be reached using the proposed algorithm.

RESULTS

The base-case analysis quantitatively compared the conventional and proposed algorithms, using values for all modeled variables and costs as discussed in the Materials and Methods and listed in Tables 1–4. In the first comparison, initial structural neuroimaging was assumed to consist of MRI without contrast, and only for patients with specific indications (in line with the previous, and best studied, AAN practice parameters (50,56)), in the proposed and conventional pathways. Under these circumstances, the financial liability accruing to each algorithm for evaluation and (mis)management of patients was similar ($3,433 and $3,564 per patient; Table 5) when calculated on the basis of costs per all patients evaluated. In other words, in terms of total dollars expended, the cost of obtaining brain PET in those patients for whom it was indicated (Fig. 2) in the proposed algorithm was comparable to the combined cost in the conventional algorithm of more needed care for patients with advancing dementia who could have benefited from earlier accurate diagnosis and treatment and of the medication prescribed to those for whom it was not indicated. Calculation of the cost-to-benefit ratios, which took account of the higher overall accuracy of the proposed algorithm (85%) compared with the conventional algorithm (69%), revealed a cost-per-benefit savings of $1,138 with the proposed algorithm ($4,047 vs. $5,185 per accurate diagnosis). Inversely, this can be viewed in terms of the number of correct diagnoses that could be made for a fixed total expenditure—for example, $100,000, for which the proposed and conventional algorithms would yield 25 and 19 accurate diagnoses, respectively. Thus, with approximately the same number of dollars spent for evaluating a given number of patients, the proposed algorithm provides more value in terms of leading more patients to appropriate management—which in turn decreases morbidity associated with the disease process and the adverse consequences (most commonly nausea and vomiting) of unnecessary medication.

As mentioned previously, the Medicare reimbursement rate for dedicated brain PET, in contrast to all other diagnostic tests included in the algorithms, had not yet been

TABLE 5
Costs and Accuracy Rates of Conventional and Proposed Algorithms in Base-Case Analysis

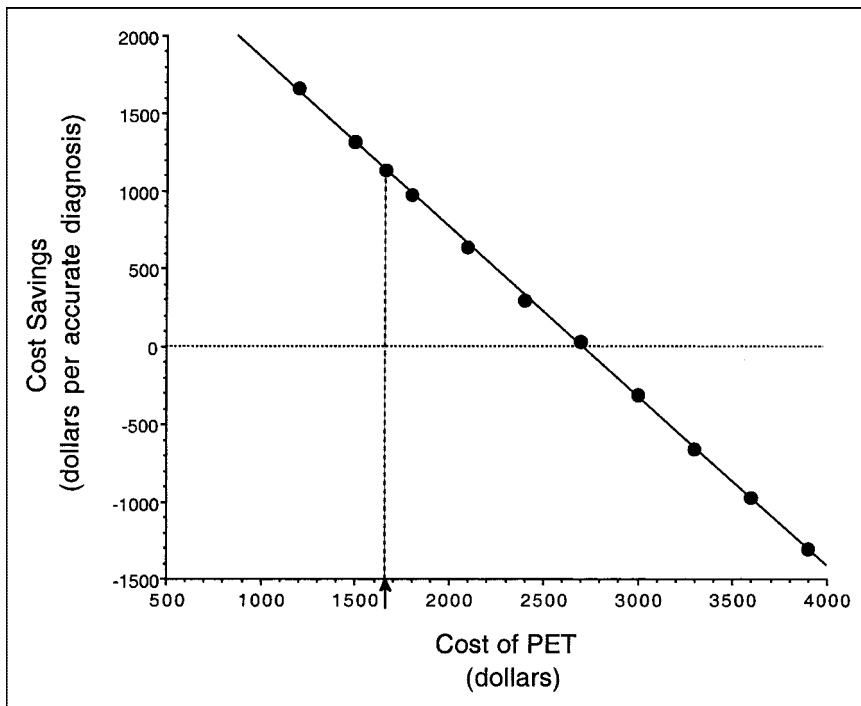| Algorithm	False-positive rate (%)	False-negative rate (%)	Mean costs per patient for evaluation and management	Overall accuracy (%)	Costs per accurate diagnosis
Conventional	23.01	8.25	$3,564	68.74	$5,185
Proposed	12.04	3.14	$3,433	84.82	$4,047
Cost savings			$131		$1,138

FIGURE 3. Effect of cost of PET on cost savings achieved with proposed algorithm. Arrow indicates PET cost ($1,661) for base case.

established at the time of this investigation. Of course, the magnitude of cost savings generated from following the proposed algorithm is directly related to the cost of PET (Fig. 3). For example, if the cost of PET were reduced from $1,661 to $1,500, cost savings would increase from $1,138 to $1,321 per accurate diagnosis; conversely, if the cost of PET went up to $1,800, cost savings would decrease to $978 per accurate diagnosis. The choice of algorithms becomes cost neutral (i.e., cost savings = $0) when the cost of PET is set at $2,728, an amount that is 64% higher than that in the base case. In other words, given the current levels of other dementia evaluation and management costs conventionally incurred, the cost for each additional correct diagnosis that will be gained through incorporation of PET into the diagnostic process will be lower than the cost that is presently incurred per correct diagnosis made, as long as the cost of a brain PET scan remains under $2,700.

We also examined the influence on cost savings of the recent update of AAN practice parameters (*38*), which made 2 essential modifications from the earlier AAN practice parameters (*56*), concerning concrete guidelines for diagnostic evaluation: (a) Structural imaging is now recommended for initial evaluation, regardless of whether specific findings are present on history and physical examination suggestive of a structural brain lesion, and (b) syphilis serology testing is no longer recommended as part of the routine blood laboratory panel. To examine the effects of those changes on our model, we ran the base-case analysis again, but with the changes introduced into both algorithms that (a) MRI without contrast was obtained for 100% of patients evaluated, and (b) the price of syphilis serology testing ($11.40) was not included in the cost for the laboratory panel. These changes increased somewhat the cost-to-benefit ratios of the proposed and conventional algorithms ($4,334 and $5,659 per accurate diagnosis, respectively) without greatly changing the relative relationship between them. Similarly, changing the original base-case analysis by obtaining MRI with and without contrast, on all patients for whom structural neuroimaging was specifically indicated, increased the cost-to-benefit ratios of the proposed and conventional algorithms by comparable amounts (to $4,553 and $5,809 per accurate diagnosis, respectively). Because this third analysis yields a cost savings for the proposed algorithm that falls intermediate to the first and second analyses ($1,256 vs. $1,138 and $1,325 per accurate diagnosis), it served as the central case around which the range-of-variable analyses were conducted.

As described in the Materials and Methods, range-of-variable analyses were performed to explore the impact of changes in the most potentially variable and critical parameters. Clearly, the accuracy achievable with PET is of critical importance to the value of the proposed algorithm. The base-case analysis used what appears to be the best estimate of that accuracy on the basis of the FIND-AD multicenter investigation (*43*). However, we also examined the effect on cost savings when sensitivity (Fig. 4, top) or specificity (Fig. 4, bottom) was varied across the entire range of estimates reported in other studies (Table 2). Even with PET operating at the lowest estimates of sensitivity, the proposed algorithm maintained a cost-to-benefit ratio comparable to that of the conventional algorithm (while still providing more total correct diagnoses than would be achieved without the use of PET). The cost savings are even more stable with respect to varying specificity: The proposed algorithm was
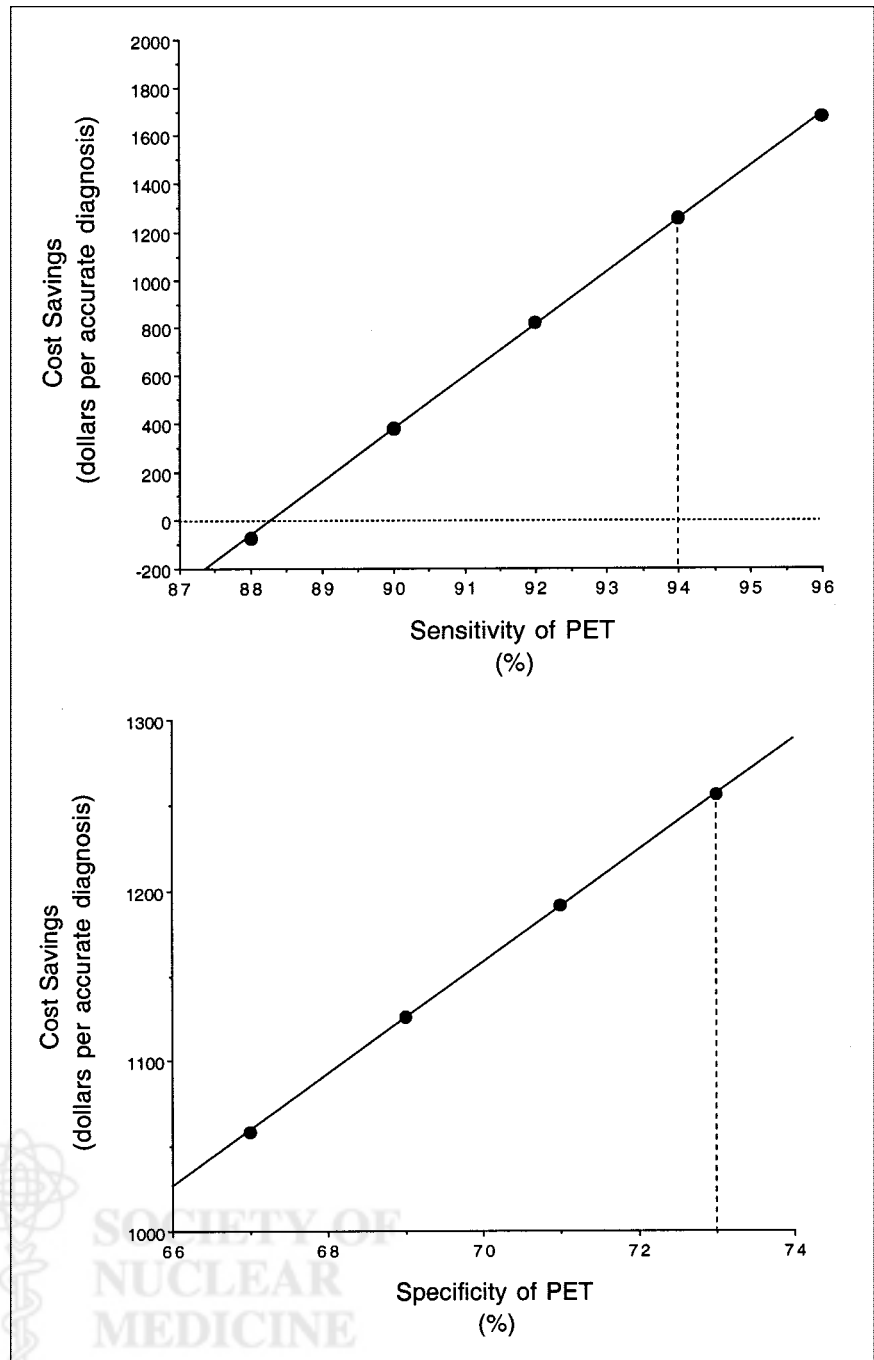
FIGURE 4. Effects of varying sensitivity (top) and specificity (bottom) of PET on cost savings achieved with proposed algorithm. Vertical dashed lines indicate sensitivity and specificity values.

associated with a cost savings of approximately $1,000 per accurate diagnosis at the lowest literature estimates of specificity for PET. Positive cost savings would in fact be maintained with the specificity of PET ranging as low as 35%. When we simultaneously penalized all 3 of the above variables in the proposed algorithm—decreasing the sensitivity to the floor literature value of 88%, dropping the specificity to the floor value of 67%, and increasing the PET base cost by 15%, to $1,910 per scan—cost savings fell to −$631 per accurate diagnosis. Under those same cost and specificity conditions, cost savings = $0 when PET sensitivity for AD was set at 90.7%.

Finally, we had used for our base case the AAN's own reported estimate of annual costs of caring for a patient with AD along with the most conservative end of the range of 9- to 18-mo delay in disease-related cognitive decline and need for institution of long-term care reported in the literature. Because this expense generates the single largest cost for an individual patient that will accrue to either algorithm, we examined the effect of varying its magnitude by allowing the estimated delay time to vary from 6 to 12 mo (or equivalently, to vary the estimated annual cost of care for an AD patient from 33% below to 33% above the AAN's estimate). As can be seen (Fig. 5), even when the estimate
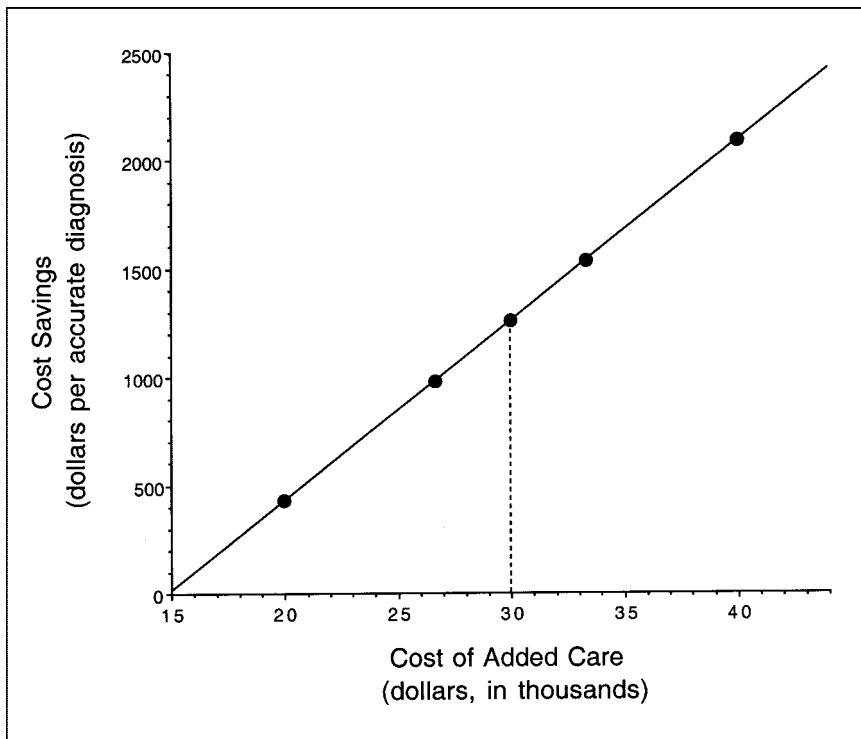
FIGURE 5. Effect of cost of added AD-related care on cost savings achieved with proposed algorithm. Vertical dashed line indicates cost of added AD care established for base-case analysis.

of added care is decreased to 6 mo (or $20,000), a cost savings of >$400 is maintained, and the proposed algorithm would provide positive cost savings with added care estimates extending from 9 mo down to less than half that time. Conversely, with an estimate of 12 mo of added care accruing, cost savings provided by the proposed algorithm exceed $2,000 per accurately diagnosed patient (and would linearly rise to still substantially higher values at the outside end of the literature reports of 18 mo of added care being needed).

DISCUSSION

As suggested by the relevant scientific literature, diagnostic work-ups that do not include assessments of cerebral metabolism tend to be substantially less sensitive in the diagnosis of AD. If one accepts the recently affirmed recommendation of the AAN (*38*) that the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria for "probable AD (rather than the more inclusive "possible AD") should be routinely used," then clinical sensitivity appears to range in the interval of 66% ± 17% and the sensitivity using PET ranges in the interval of 91% ± 3% (Tables 2 and 3). The sensitivity of clinical evaluation can be increased to 90.5% ± 5.5% (comparable to that using PET) by expanding the diagnosis of AD to include patients who meet NINCDS–ADRDA criteria for possible AD, and including moderately and severely advanced dementia cases in the analysis, but at the expense of specificity (55.5% ± 5.5% in the class I

studies). In contrast, at that level of sensitivity, the specificity using PET is 70% ± 3%.

The AAN Quality Standards Subcommittee also reviewed 9 studies that addressed the clinical diagnostic accuracy of AD but that were classified as having lower "quality of evidence" than those described in Table 3. Across all of these studies, they found an average clinical specificity of 70% (as occurs with PET), whereas average sensitivity in that analysis was 81% (compared with the 91% ± 3% reported for PET). In the 2 largest class II studies that uniformly used NINCDS–ADRDA diagnostic criteria (*69,70*), at a sensitivity of 90% ± 1% (achieved by including possible AD patients and moderately advanced dementia cases), specificity fell to 29% ± 8%.

With a preponderance of evidence pointing to improving diagnostic accuracy by incorporating FDG PET into the algorithm for evaluation of dementia, the focus then turns to the question of exactly when the PET study should be obtained. Beyond the specific advantages conferred by more accurate diagnoses leading to more appropriate management (Introduction), other ramifications of having the added information provided by PET bear on this issue. For example, if accurate positive diagnoses are achieved early on, patients and their families can be spared the repeated batteries of diagnostic tests often performed over extended periods of time, and they and their physicians would less often experience the frustrations of ambiguous diagnostic conclusions. The information would also help families to plan for issues important to future patient care—particularly so, in light of recent data indicating that the degree of

hypometabolism identified by PET in certain affected brain regions predicts the rate of future cognitive decline, as assessed by standardized measures of memory in the years subsequent to PET examination (71).

These and other considerations support the notion that the best time to obtain the PET study is early in the course of the clinical work-up, as soon as it has been determined that the patient is an appropriate candidate for evaluation of cerebrocortical dysfunction. The guiding principle for that determination is simply as follows: A patient who presents with an adverse change in cognition or behavior, which has not been fully explained and fully reversed following prompt and standard diagnostic and treatment approaches, should undergo PET imaging (Fig. 2).

How much will following such an algorithm cost us and, more to the point, how does that compare with the costs incurred when we do not have available the additional information provided by PET? The cost associated with performance of a dedicated brain PET scan amounts to less than the typical costs of 1 y of pharmacotherapy for unnecessary treatment of a patient misdiagnosed with AD or 1 mo of lost productivity and independence of a patient for whom we fail to provide timely diagnosis and treatment. In the present decision analysis, it was found that the added diagnostic accuracy obtained by incorporation of FDG PET into the routine clinical evaluation of patients presenting with early symptoms of dementia could be achieved in an economically practical manner. This was true for the base-case situation, despite that analysis being conservatively biased in 2 important ways: (a) by assuming that reported diagnostic accuracy, based on using conventional means and observing patients over an average of 3 y, could be achieved with equal accuracy after only 6 mo of conventional evaluation; and (b) by assuming that only 9 mo of delay in disease progression would occur from failure to diagnose and treat AD, in the face of the literature reporting a range of 9–18 mo for this. Furthermore, the economic viability of the proposed algorithm was maintained when values were varied widely beyond those of the base-case analysis, affecting the manner in which structural imaging was used as well as the cost, sensitivity, and specificity of PET and the cost of added care for AD patients.

A recent cost-effectiveness study by McMahon et al. (72) modeled the role of SPECT and specialized MRI in the management of AD. The authors concluded that the addition of functional neuroimaging to the usual diagnostic regimen for evaluating AD was not cost-effective. Their study differed in several important ways from our analysis. First, it did not focus on early diagnosis but assumed a patient population in which 40% of the AD patients had already advanced to a moderate stage of disease. Second, patients who were thought to be clinically unlikely to have AD were not offered SPECT in their model, thereby forfeiting in advance the opportunity for nuclear imaging to detect unsuspected cases. Third, costs were not compared on the basis of diagnostic accuracy achieved, as in this analysis, but rather on the basis of quality-adjusted life years that were estimated to "accrue to hypothetical cohorts of patients." Other differences included the assumption in the McMahon et al. study of a base-case diagnostic specificity for conventional work-up of 90% (much higher than in this analysis or than that estimated by the AAN (38)) and, of course, no explicit incorporation of PET into any of its algorithms.

It may be observed that the conventional algorithm depicted here, derived especially from AAN recommendations, appears (understandably) to be formulated with an orientation pointed primarily toward neurologists approaching dementia patients, whereas we formulated the proposed algorithm with an orientation pointed primarily toward primary care physicians. With respect to effect on the analysis, however, this was more a matter of style than substance, and we expect that neurologists and primary care physicians will be able to navigate through the evaluation process guided by either algorithm and that similar costs should accrue to a given algorithm when appropriately skilled physicians of any specialty are doing that navigating. A major motivating factor for the orientation we have taken, however, is that regardless of the potential benefits of 1 diagnostic algorithm versus another, the more fundamental problem at this time is the failure of physicians to attempt to identify or diagnose dementia at all (73–75). Although several professional organizations and consensus groups, as well as the U.S. Public Health Service, have recommended formal dementia screening for elderly primary care patients (76–79), most clinicians lack training in the use of cognitive screening tests (80–84), and fewer than 1 in 8 physicians actually administers such tests (83).

The problem is further confounded by some physicians' fears of the psychologic effects of diagnosing a patient with early dementia. However, the published evidence indicates that such concerns of physicians are often out of step with the desires and needs of their patients. Many families consider their doctors to be reticent in making the diagnosis of dementia and feel that physicians may minimize the associated problems (84). One survey of 156 community-dwelling older persons revealed that 80% of them preferred to be informed if they had dementia (85). In another study, >90% of 224 consecutive patients in an ambulatory practice said that if their physician thought they had AD, they would want to be told (86). Nor are such paternalistic concerns unique to health care providers: In a survey in which 71% of respondents indicated that they would want to be informed of the diagnosis should they develop AD, only 17% of these same individuals stated they would want their family members with that diagnosis to be informed of it (87). In light of the accumulated evidence that patients benefit significantly by accurate diagnosis followed by institution of appropriate management in the early stages of disease, it may not be long before failure to diagnose AD in a patient presenting with suggestive signs and symptoms of cognitive decline may come to be viewed similarly to the way that failure to

diagnose malignancy in the face of suggestive evidence that is discovered (or should have been discovered) on history or examination is currently viewed. Once the importance of making an accurate diagnosis in patients with dementia becomes more widely appreciated, application of the most sensitive and accurate tools available for that task will likely become more common.

CONCLUSION

As AD is increasingly recognized as a pharmacologically treatable dementia, it is becoming less tenable to take a watchful waiting approach to making this diagnosis; because more advanced AD may be less amenable to therapy, even a 1-y delay in reaching a therapeutic decision may compromise care. The availability of PET for imaging brain metabolic activity, allowing sensitive detection of neurodegeneration at a very early stage, raises the prospect that patients can be steered toward more appropriate management earlier in the course of their disease. This prospect particularly deserves consideration now that recent developments in instrumentation and radiopharmaceutical distribution have made obtaining scans of cerebral metabolism achievable in routine clinical settings—and for less than the cost of a single month of the 9–18 mo of extra care that typically is needed for a patient who is not diagnosed (and thus not treated) in a timely manner. Analysis of the models of evaluation and management presented in this article predict that improved care can be economically achieved through appropriate incorporation of PET into the diagnostic work-up.

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