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Stability of Clinical Etiologic Diagnosis in Dementia and Mild Cognitive Impairment: Results from a Multi-Center Longitudinal Database

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Abstract

Many new therapies for dementia target a specific pathologic process and must be applied early. Selection of specific therapy is based on the clinical etiologic diagnosis. We sought to determine stability of the clinical etiologic diagnosis over time and to identify factors associated with instability.

We identified 4,141 patients with dementia or mild cognitive impairment who made at least two visits approximately a year apart to a dementia research center, receiving a clinical etiologic diagnosis on each visit. We assessed concordance of etiologic diagnoses across visits, kappa statistics, and transition probabilities among diagnoses.

The primary clinical etiologic diagnosis remained stable for 91% of patients, but with a net shift toward dementia with Lewy bodies and Alzheimer disease. Lower diagnostic stability was significantly associated with older age, nonwhite race, milder disease at presentation, more underlying conditions contributing to cognitive decline, lack of a consistent spouse/partner informant, and being evaluated by different clinicians on different visits. Multi-state Markov modeling generally confirmed these associations.

Clinical etiologic diagnoses were generally stable. However, several readily ascertained characteristics were associated with higher instability. These associations may be useful to clinicians for anticipating when an etiologic diagnosis may be more prone to future change.

Keywords

dementia diagnosis; diagnosis stability; dementia etiology

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INTRODUCTION

Dementia can result from any of several underlying disease processes, including Alzheimer disease, Lewy body disease, frontotemporal dementia, cerebrovascular disease, and other less common disorders¹. Much current research is aimed at finding effective ways to prevent or treat dementia, and most drugs in development are aimed at a specific etiologic type of dementia. For example, experimental vaccines have been developed to stimulate immune-system clearance of amyloid protein in Alzheimer disease²³. Other drugs seek to block accumulation of α -synuclein, which leads to Lewy body disease⁴⁵. Gene therapy has been proposed to counteract a genetic abnormality that leads to hyperphosphorylated tau protein in frontotemporal dementia⁶. Drugs to inhibit platelet aggregation may prevent progression of vascular dementia⁷⁸.

Many new drugs may need to be given quite early in the disease course, before widespread neuronal loss occurs, to be effective⁹¹⁰. Because neuropathological confirmation of a dementia diagnosis is rarely possible during life, selection of an appropriate disease-specific drug must almost always depend on a *clinical* etiologic diagnosis, based on symptoms, signs, and test results, none of which have perfect sensitivity and specificity. The clinical etiologic diagnosis is the underlying neurodegenerative process to which the physician ascribes the patient's neurocognitive abnormalities—for example, Alzheimer's disease, cerebrovascular disease, or Lewy body disease, among others. Often the accuracy of that clinical etiologic diagnosis will not be known until autopsy. However, due to the chronic and progressive nature of most dementing illnesses, the true underlying condition itself is unlikely to change over time. Thus, if there are inconsistencies in the clinical diagnosis over time for the same patient, it is unlikely that all of those different diagnoses are correct. Thus, *consistency* or *stability* of the clinical etiologic diagnosis can be regarded as a necessary but not sufficient requirement for accuracy.

This study had three aims: (1) to quantify the stability of clinical etiologic diagnoses over time in a large sample of patients with cognitive impairment; (2) to describe changes in the distribution of etiologic diagnoses over time; and (3) to identify factors associated with greater instability of the clinical etiologic diagnosis.

METHODS

Setting

Study subjects were drawn from all 32 Alzheimer's Disease Centers (ADCs) funded by the U.S. National Institute on Aging. These centers conduct research and provide clinical evaluation and treatment for patients with mild cognitive impairment (MCI) or cognitive impairment from Alzheimer disease or other forms of dementia. The Uniform Data Set (UDS), a set of standardized data collection forms and guidelines, was used at all centers¹¹. Data collection was overseen by the National Alzheimer's Coordinating Center, which also served as a common data repository. The present analysis was approved by the University of Washington Institutional Review Board. Informed consent was obtained from all participants.

Study subjects

We studied 4,141 ADC patients who were judged clinically to have either MCI or dementia. All were evaluated approximately annually. For this study, a patient had to have made at least two UDS visits about a year apart between September, 2005 and November, 2009, at which a clinical etiologic diagnosis of cognitive impairment had been recorded. The first study visit for each patient was when he/she first was recorded as having dementia or MCI.

Some patients had made up to five annual visits thereafter, depending on their date of enrollment and retention in study.

Data

The UDS data collection forms allowed any of 21 different etiologies to be recorded, either as the primary clinical diagnosis or as a contributing condition. Written guidelines for use with UDS forms (available at <http://www.alz.washington.edu>) incorporated diagnostic criteria for several etiologic diagnoses for which explicit criteria have been developed, after review and approval by the UDS Clinical Task Force [11]. The UDS did not mandate that each patient receive specific imaging procedures or biomarker tests, several of which were performed as part of center-specific clinical research protocols and not at all centers.

Characteristics evaluated as possible risk factors for diagnostic instability included demographic factors (age, gender, and race); severity of cognitive impairment at presentation and time since first symptoms began; presence or absence of other comorbid conditions; whether multiple dementing illnesses were thought to be contributing to cognitive decline; type of informant who accompanied the patient to ADC visits; whether the patient was evaluated by the same clinician on each visit or by different clinicians; and whether the clinical etiologic diagnosis was assigned by a single clinician or through a consensus process after the visit.

Analysis

Many of the 21 possible etiologic diagnoses proved to be rare. Accordingly, etiologic diagnoses were grouped in two ways, resulting in an 8-category list and a 4-category list. The 8-category list included: Alzheimer disease (AD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), primary progressive aphasia (PPA), Parkinson's disease (PD), vascular dementia (VaD), other etiology (Other), or unknown etiology (Unknown). The shorter 4-category list included AD, DLB, FTD and other/unknown. Each patient fell into one category on each list at each visit, based on the primary etiologic diagnosis recorded at that visit.

Initial descriptive analyses involved cross-tabulating the primary etiologic diagnosis from visit 1 with that from visit 2. Changes in the overall (marginal) distribution of diagnoses across successive visits were also examined.

Considering two successive visits for each patient, one measure of etiologic-diagnosis stability is the proportion of patients who received the same etiologic diagnosis on both visits---a measure known as *concordance*. However, our main measure of stability was instead the kappa statistic¹², which corrects for the amount of agreement expected by chance if a diagnosis were simply chosen at random from the overall distribution of etiologic diagnoses at each visit. Kappa statistics were then compared among subgroups defined by the potential risk factors for diagnostic instability listed earlier.

Comparisons of kappa between exposure groups can be confounded if the groups differ on other factors that also affect etiologic-diagnosis stability. We developed a relatively simple method to control for other key patient characteristics by applying inverse-probability-of-exposure weights. Let E be a categorical exposure variable and e_i its observed value for person i . Let X be a vector of potential confounders (covariates) and x_i be the vector of observed values on X for person i . An adjustment weight w_i for person i was defined as

$$w_i = \frac{1}{\Pr(E=e_i|X=x_i)}$$
 as estimated by logistic regression if E was binary or by multinomial logistic regression if E had more than two possible values. Kappa was then computed as

usual, weighting each observation by w_i . This approach was borrowed from work on marginal structural models in epidemiology¹³¹⁴. Here, the adjusted kappa value for a given exposure group can be interpreted as the value that would have been obtained if that group had had the same covariate distribution as the full study sample. The bootstrap method¹⁵ was used to obtain estimated standard errors for adjusted kappa across 1,000 bootstrap samples.

Finally, discrete-time Markov models¹⁶¹⁷ were applied. Let Y_{ij} denote the etiologic diagnosis (“state”) that person i was in on visit j , and X_{ij} the corresponding vector of predictors. Let $\pi_{ijk\tilde{k}} = \text{PR}(Y_{ij} = k | Y_{i,j-1} = \tilde{k}, X_{ij})$ denote the probability that patient i was in state k on visit j after having been in state $\tilde{k}$ on the previous visit. The multinomial logit

model was then $\ln\left(\frac{\pi_{ij\tilde{k}k}}{\pi_{ijkk}}\right) = X'_{ij}\beta_{\tilde{k}k}$, where $\beta_{\tilde{k}k}$ is the coefficient vector from state $\tilde{k}$ to state k . The left side of this equation can be seen to be the log of the ratio of two probabilities: the probability of moving from state $\tilde{k}$ to state k , divided by the probability of remaining in state k , modeled as a linear function of the covariates. An adjusted risk ratio was then obtained for each covariate value by exponentiating its estimated beta-coefficient, and confidence limits were obtained from its estimated standard error. For this analysis, each pair of consecutive visits was treated as one possible transition. Thus, if a patient made several visits, he or she contributed several observations, which were treated as independent (conditional on the covariates) under a first-order Markov assumption.

Results

Table 1 shows how the primary clinical etiologic diagnoses on visit 1 corresponded to those on visit 2, using the 8-category grouping scheme. The top panel shows the number of subjects in each cell; the bottom panel shows the percent distribution of etiologic diagnoses at visit 2 among patients with each etiologic diagnosis at visit 1. Not surprisingly, AD was the most common form of dementia, and most patients received that etiologic diagnosis on each visit. Most patients kept the same diagnosis on both visits, but those with an initial diagnosis of frontotemporal dementia (FTD), vascular dementia (VaD), or “other” were more likely to receive a different diagnosis the following year, compared with other patients. Overall, the concordance was 0.91, with a kappa value of 0.77, representing substantial agreement beyond chance. Grouping into only four diagnosis categories made little difference to these results (concordance = 0.92, $\kappa = 0.78$).

Comparing the row and column totals in the top panel of Table 1 shows that the overall distribution of primary clinical etiologic diagnoses remained similar from visit 1 to visit 2. Nonetheless, given the large sample, some changes were statistically significant. Dementia with Lewy bodies (DLB) and Alzheimer disease (AD) both gained “market share,” and for DLB, the shift was statistically significant ($p = 0.007$). The diverse “other” category decreased significantly ($p = 0.047$). Additional analyses not shown revealed that similar trends in the mix of diagnoses continued to visit 3 in the smaller subset of patients who had made three or more annual visits.

For many patients, other disease processes besides the primary one were recorded as also contributing to a patient’s cognitive impairment. Table 2 shows concordance and kappa statistics for whether each of 21 disease processes was mentioned as involved (as either a primary or contributing cause) on visits 1 and 2. These process-specific concordances were generally high, but the corresponding kappa statistics were more variable. Lower kappas were observed for dementing processes of a more transitory nature, such as depression ($\kappa = 0.47$), medical illness ($\kappa = 0.44$), psychiatric illness ($\kappa = 0.38$), and medication effects ($\kappa = 0.25$).

Using kappa as the measure of diagnosis stability between visits 1 and 2, several statistically significant differences were found among subgroups of patients (Table 3). Diagnosis stability was higher in younger patients and lower in older ones. Kappa was also higher in patients of white race than in Blacks or patients of other races. In light of these demographic differences, the kappa statistics for other characteristics were adjusted for age and race. No statistically significant association was found with education, before or after adjustment for age and race. Etiologic diagnoses tended to be less stable among patients with less severe disease at visit 1, as reflected by having MCI rather than dementia or a Clinical Dementia Rating less than 1. Those with an MMSE score greater than 24 at visit 1 also had less-stable clinical etiologic diagnoses, but not to a statistically significant extent. Little association was found with length of time between onset of symptoms and visit 1. Diagnostic stability tended to be lower among patients who were judged to have more underlying disease processes contributing to their cognitive decline. The type of informant who accompanied the patient at clinic visits also mattered: diagnostic stability was highest when the informant was the patient's spouse or live-in partner on both visits and lowest when two different informants (one of them not a spouse or partner) accompanied the patient. The etiologic diagnosis was less stable if two different clinicians evaluated the patient on successive clinic visits, rather than the same clinician both times. However, there was little association between stability of the etiologic diagnosis and whether the diagnosis was assigned by an individual clinician or via a consensus process on visit 1.

Presenting full results from multi-state Markov modeling is difficult because of the large volume of numerical data. Even using only 8 diagnostic categories, 56 transitions from one diagnostic state to another are possible, resulting in 56 logistic regression models, each of which includes multiple coefficient estimates and associated standard errors. Instead, a summary of results is shown in Table 4 for the 4-category diagnostic grouping scheme, which involves 12 possible transitions. In this analysis, all pairs of consecutive visits for each patient were included, not just the first two visits. Following the visit at which each patient had first been recorded as having MCI or dementia, 2,269 patients made one subsequent visit, 1,266 made two, 558 made three, 17 made four, and 1 made five. The nine covariates shown in the first column were included in all models. For each covariate value except the reference category, a 4×4 table is shown at right. Each number within that table can be interpreted as the adjusted risk ratio of transitioning from the row diagnosis (made at the earlier visit of the pair) to the column diagnosis (at the later visit) for patients with that covariate value. For example, the value of 2.11 in the DLB row and AD column for age 80+ means that, relative to a patient age <70 years (the reference age category), a patient age 80+ years was 2.11 times more likely to transition from DLB on the earlier visit to AD on the later visit, adjusting for all other covariates shown in the table. A box around an estimate denotes that it was statistically significantly different from 1.0.

For age, most risk ratio estimates were statistically significantly different from 1.0, suggesting that age was quite important as a predictor of most of the possible transitions. The risk ratio estimates uniformly greater than 1.0 in the first column suggest that advanced age favored a net shift toward a diagnosis of AD over successive visits. A roughly similar pattern is seen for DLB in the second column, suggesting that age favored a shift in diagnosis toward DLB (unless the patient had a diagnosis of AD).

Among the other covariates in Table 4, the Clinical Dementia Rating (CDR) on the earlier visit appeared quite important as a predictor of several transitions in diagnosis. Relative to patients with CDR <1, higher CDR scores favored net migration out of the diverse "Other" category and net migration into the FTD category. The number of contributing conditions also appeared important, but with a more complex pattern. Patients with more contributing conditions tended to shift away from an initial diagnosis of AD toward DLB, FTD, or Other.

DLB in particular tended to “win out” and become the primary diagnosis on the later visit in patients with multiple contributing conditions.

A pertinent negative finding is the absence of statistically significant adjusted risk ratios for the last covariate shown, the UDS visit numbers that corresponded to the sequence of consecutive visits used in this analysis. This pattern suggests that pooling data across pairs of successive visits, regardless of when those visits occurred in a patient’s UDS participation history, was a defensible analytic strategy.

Finally, Table 5 shows how the primary clinical etiologic diagnosis compared with the primary neuropathological diagnosis for the subgroup of 526 (13%) study patients who died and underwent brain autopsy. Separate panels are shown for the primary clinical etiologic diagnosis on clinic visits 1 and 2. In general, agreement between clinical and neuropathological diagnoses was high but not perfect, and slightly better if the clinical diagnosis came from visit 2 rather than visit 1. Note, however, that these results concern only the non-random subsample who died and underwent brain autopsy, and that the elapsed time between clinical visits and death could have been up to several years.

Comment

Using data on over 4,000 patients evaluated on two or more annual visits at 32 dementia research centers in the U.S., we found that the primary clinical etiologic diagnosis remained stable for about nine out of ten patients. Nonetheless, there was a gradual shift in the distribution of etiologic diagnoses, with an increasing share of patients diagnosed as having DLB or AD. Moreover, we found several subgroups in whom the clinical etiologic diagnosis was significantly less stable, as reflected by a lower kappa statistic. Clinical etiologic diagnoses were less stable in older patients, nonwhites, those with clinically milder disease at presentation, those judged to have more etiologic processes contributing to cognitive decline, patients unaccompanied by a spouse or partner to serve as informant, and those who were evaluated by different clinicians on different visits.

Results of multi-state Markov modeling are harder to summarize but generally supported the importance of the same factors as affecting the likelihood of transition from one etiologic diagnosis to another. This observed pattern of associations may help to identify patients with early dementia in whom the clinical etiologic diagnosis is more likely to change over time, which may in turn affect the balance of risks and benefits of early therapies aimed at a specific underlying pathologic process.

To our knowledge, no previous published studies have examined the stability of clinical etiologic dementia diagnosis in relation to the characteristics studied here. The demographic factors that we found to be associated with lower stability—older age and nonwhite race—may simply be markers for other underlying causal factors. It has been suggested [18] that informants for older or African American dementia patients may be less available and/or knowledgeable than for other groups.

Two factors associated with stability of the clinical etiologic diagnosis may be of special interest because they are potentially modifiable. First, having a spouse or partner accompany the patient at both visits was associated with greater diagnostic stability. This finding suggests that someone who is in constant close contact with the patient can provide better and more consistent information about disease manifestations, leading to a more stable (and possibly more accurate) diagnosis. These results thus provide empirical support for the importance of obtaining information from a knowledgeable informant in clinical evaluation of patients with early dementia¹⁸¹⁹.

Second, the primary etiologic diagnosis was less likely to change if the same clinician evaluated the patient on repeated visits. This result suggests that individual clinicians may be reluctant to change their own initial diagnostic impressions, or that a “second opinion” can often lead to re-thinking and changing a patient’s clinical etiologic diagnosis. But despite recently published preliminary evidence that a consensus diagnostic process involving multiple evaluators can yield improved accuracy over diagnoses assigned by individual experts²⁰, we found no significant difference in stability of the etiologic diagnosis in relation to whether a consensus diagnostic process was used.

The finding that diagnostic stability was higher for patients with dementia than for those with MCI agrees with the common clinical observation that classic manifestations of a disease often become more apparent as the disease progresses. This pattern may be especially true of neurodegenerative diseases, which can evolve over many years. It may pose a challenge for clinicians, however: even though etiologic diagnosis of MCI may be more subject to change, therapies aimed at slowing particular forms of neurodegeneration may need to be applied at the MCI stage to be effective.

In interpreting results of this study, it should be kept in mind that *consistency* of the clinical etiologic diagnosis is not the same as *accuracy* of that diagnosis. An etiologic diagnosis can be consistent across clinical encounters but consistently wrong. The “gold standard” for accuracy of an etiologic diagnosis remains neuropathology, which unfortunately is available only on a subset of a subset of patients with dementia: namely, those who die and then undergo brain autopsy. The present study focused instead on diagnostic stability, which could be addressed in a larger patient population. Future advances in imaging and biomarker development will almost certainly lead to new research opportunities to investigate accuracy in live patients, as well as to improvements in diagnostic stability and accuracy themselves²¹. Nonetheless, even the most recently revised criteria for Alzheimer disease rely on clinical features, treating evidence from biomarkers as complementary but not required¹⁰.

Other study limitations should also be noted. Patients at participating ADCs are best regarded as a large clinical case series, not a truly population-based sample, so generalizability of these findings is uncertain. Although the content of the UDS was standardized across centers, use of imaging modalities and biomarkers varied among centers, depending in part on each center’s own research focus. Most disease-specific drugs are still under development, and we do not yet know what the consequences might be of using such a drug when the clinical etiologic diagnosis is incorrect.

These limitations notwithstanding, it is reasonable to expect that the stability and accuracy of the clinical etiologic diagnosis for dementia will be increasingly important for proper treatment. Information about risk factors for diagnostic instability, such as that generated in this study, can help clinicians to identify patients in whom an early diagnosis may be most likely to change, and it can help alert researchers to possible diagnostic misclassification.

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Table 1

Cross-tabulation of Primary Diagnosis (in 8 Groups) at Visit 1 and Visit 2 for All Subjects

Visit 1	Visit 2							
	AD	DLB	FTD	PPA	PD	VaD	Other	Total
Counts:								
AD	3,038	36	14	9	4	22	29	20
DLB	17	158	1	0	5	1	1	0
FTD	20	1	154	13	0	0	7	5
PPA	8	0	11	100	0	0	3	1
PD	3	6	0	0	108	0	1	1
VaD	37	1	0	0	0	72	0	0
Other	49	3	2	3	0	2	103	8
Undet	24	2	3	1	0	4	4	26
Total	3,196	207	185	126	117	101	148	61
Row percents:								
AD	95.8	1.1	0.4	0.3	0.1	0.7	0.9	0.6
DLB	9.3	86.3	0.5	0.0	2.7	0.5	0.5	0.0
FTD	10.0	0.5	77.0	6.5	0.0	0.0	3.5	2.5
PPA	6.5	0.0	8.9	81.3	0.0	0.0	2.4	0.8
PD	2.5	5.0	0.0	0.0	90.8	0.0	0.8	0.8
VaD	33.6	0.9	0.0	0.0	0.0	65.5	0.0	0.0
Other	28.8	1.8	1.2	1.8	0.0	1.2	60.6	4.7
Undet	37.5	3.1	4.7	1.6	0.0	6.2	6.2	40.6

Concordance = 0.91 Kappa = 0.77 (0.75 – 0.79)

AD = Alzheimer disease; DLB = dementia with Lewy bodies, FTD = frontotemporal dementia; PPA= primary progressive aphasia; PD = Parkinson's disease; VaD= vascular dementia

Table 2

Reliability of Whether Each of Several Etiologies Was Judged To Be Involved, Either as a Primary or Contributing Cause of Cognitive Impairment, Across Two Consecutive UDS Visits

Etiology	Number of subjects for whom etiology was listed as involved on:				Concordance	Kappa	
	Both visits	Visit 1 only	Visit 2 only	Neither visit		Est.	(95% CI)
Alzheimer disease	3,186	117	158	680	0.93	0.79	(0.77–0.81)
Lewy bodies	220	38	74	3,809	0.97	0.78	(0.74–0.82)
Frontotemporal	179	64	47	3,851	0.97	0.75	(0.70–0.79)
Primary progressive aphasia	123	33	30	3,955	0.98	0.79	(0.74–0.84)
Parkinson's disease	145	13	30	3,953	0.99	0.87	(0.83–0.91)
Vascular	228	89	95	3,729	0.96	0.69	(0.65 – 07.3)
Corticobasal degeneration	45	14	15	4,067	0.99	0.75	(0.67–0.84)
Depression	261	237	218	3,425	0.89	0.47	(0.43 –05.1)
Progressive supranuclear palsy	19	4	8	4,110	1.00	0.76	(0.63–08.9)
Traumatic brain injury	14	10	14	4,103	0.99	0.54	(0.37–07.0)
Illness-induced	29	31	40	4,041	0.98	0.44	(0.33–0.55)
Alcohol-related	16	17	8	4,100	0.99	0.56	(0.40–0.71)
Psychiatric illness	11	19	16	4,095	0.99	0.38	(0.22–0.54)
Hydrocephalus	17	5	7	4,112	1.00	0.74	(0.59–0.88)
Prion	4	1	0	4,136	1.00	0.89	(0.67–1.11)
Down's syndrome	3	0	1	4,137	1.00	0.86	(0.58–1.13)
Medication-induced	8	21	25	4,087	0.99	0.25	(0.11–0.40)
Huntington's	1	0	0	4,140	1.00	1.00	(1.00–1.00)
Neoplasm	2	3	2	4,134	1.00	0.44	(0.04–0.85)
Other	75	91	92	3,883	0.96	0.43	(0.36–0.50)
Undetermined	30	52	38	4,021	0.98	0.39	(0.29–0.49)

Table 3

Stability of Etiologic Diagnosis from Visit 1 to Visit 2 by Selected Exposures, Before and After Adjustment for Age and Race

Characteristic	n	Unadjusted		Adjusted for age and race		p
		Kappa	(95% CI)	Kappa	(95% CI)	
Age (years)						<.001
<70	1,123	0.82	(0.79–0.85)			
70–79	1,616	0.75	(0.71–0.79)			
80+	1,402	0.64	(0.58–0.70)			
Race						<.001
White	3,082	0.81	(0.79–0.83)			
Black	399	0.63	(0.53–0.74)			
Other	660	0.57	(0.50–0.65)			
Education						0.6
<High school	455	0.70	(0.61–0.79)	0.73	(0.63–0.83)	
High school grad	939	0.78	(0.74–0.83)	0.79	(0.75–0.83)	
Beyond high school	2,354	0.80	(0.77–0.83)	0.79	(0.76–0.81)	
Cognitive status (visit 1)						0.002
MCI	557	0.66	(0.61–0.71)	0.70	(0.64–0.75)	
Demented	3,584	0.79	(0.77–0.82)	0.79	(0.77–0.81)	
Global CDR (visit 1)						0.006
<1	1,618	0.73	(0.70–0.77)	0.74	(0.70–0.77)	
1	1,780	0.79	(0.75–0.82)	0.78	(0.74–0.82)	
2+	743	0.83	(0.78–0.87)	0.83	(0.78–0.87)	
MMSE (visit 1)						0.11
<24	2,217	0.79	(0.75–0.82)	0.79	(0.75–0.81)	
24+	1,805	0.75	(0.72–0.78)	0.75	(0.72–0.78)	
Years since symptom onset						0.9
<2	374	0.77	(0.71–0.84)	0.78	(0.72–0.85)	
2–4.9	1,554	0.79	(0.76–0.83)	0.79	(0.75–0.82)	
5+	1,742	0.77	(0.74–0.80)	0.77	(0.74–0.80)	
No. of contributing conditions						<.001
0	3,037	0.81	(0.78–0.83)	0.81	(0.78–0.83)	

Characteristic	Unadjusted			Adjusted for age and race		
	n	Kappa	(95% CI)	p	Kappa	(95% CI)
1	869	0.71	(0.67–0.76)		0.72	(0.67–0.76)
2+	235	0.65	(0.57–0.74)		0.66	(0.58–0.74)
Modified Charlson comorbidity score				0.6		
0	3,445	0.77	(0.75–0.80)		0.77	(0.74–0.79)
1	595	0.75	(0.69–0.82)		0.79	(0.73–0.84)
2+	66	0.71	(0.54–0.88)		0.79	(0.62–0.92)
Type of informant				<.001		0.003
Spouse/partner both times	2,472	0.81	(0.78–0.83)		0.79	(0.77–0.82)
Spouse/partner once, other once	162	0.62	(0.48–0.75)		0.63	(0.50–0.75)
Other informant both times	1,370	0.67	(0.62–0.72)		0.72	(0.68–0.77)
How diagnosis made				0.13		0.3
Clinician	913	0.74	(0.69–0.78)		0.74	(0.69–0.79)
Consensus	3,228	0.78	(0.75–0.80)		0.77	(0.75–0.80)
Same clinician both times?				0.004		0.015
No	2,013	0.75	(0.72–0.79)		0.76	(0.73–0.79)
Yes	1,808	0.82	(0.79–0.85)		0.81	(0.78–0.84)

Markov Model Results: Adjusted Risk Ratios for Transitioning from One Clinical Etiologic Diagnosis (in 4 Categories) to Another between Adjacent Visits

Table 4

Characteristic	Earlier visit diagnosis	Later visit diagnosis			
		AD	DLB	FTD	Other
Age (years)					
<70		(Reference)			
70–79	AD	—	0.84	0.18	0.39
	DLB	1.18	—	0.21	0.46
	FTD	5.59	4.71	—	2.19
	Other	2.54	2.15	0.46	—
80+	AD	—	0.47	0.05	0.25
	DLB	2.11	—	0.10	0.53
	FTD	20.44	9.70	—	5.13
	Other	3.99	1.90	0.20	—
Gender					
Male		(Reference)			
Female	AD	—	0.37	0.43	0.83
	DLB	2.69	—	1.16	2.23
	FTD	2.31	0.86	—	1.92
	Other	1.20	0.45	0.52	—
Race					
White		(Reference)			
Black	AD	—	0.38	0.23	0.50
	DLB	2.64	—	0.61	1.32
	FTD	4.30	1.64	—	216
	Other	1.99	0.76	0.46	—
Other	AD	—	0.54	0.10	0.68
	DLB	1.85	—	0.19	1.27
	FTD	9.62	5.21	—	6.58
	Other	1.47	0.79	0.15	—
Education					

Characteristic	Earlier visit	Later visit diagnosis			
	diagnosis	AD	DLB	FTD	Other
Less than high school		(Reference)			
	AD	—	1.93	1.42	1.33
	DLB	0.52	—	0.74	0.69
	FTD	0.71	1.36	—	0.94
High school graduate	Other	0.75	1.45	1.07	—
	AD	—	1.52	1.33	1.30
	DLB	0.66	—	0.88	0.86
	FTD	0.76	1.14	—	0.99
Beyond high school	Other	0.77	1.16	1.02	—
		(Reference)			
	AD	—	0.75	1.20	0.34
	DLB	1.33	—	1.59	0.45
CDR = 1	FTD	0.84	0.63	—	0.28
	Other	2.96	2.23	3.55	—
	AD	—	1.96	4.06	0.33
	DLB	0.51	—	2.08	0.17
CDR = 2+	FTD	0.24	0.48	—	0.08
	Other	3.00	5.88	12.24	—
		(Reference)			
	AD	—	0.89	0.97	0.78
<2	DLB	1.13	—	1.09	0.88
	FTD	1.05	0.93	—	0.82
	Other	1.28	1.14	1.24	—
	AD	—	0.64	0.99	0.93
2–4	DLB	1.55	—	1.55	1.45
	FTD	1.02	0.66	—	0.95
	Other	1.07	0.69	1.06	—
	5+		(Reference)		
Years since onset	AD	—	0.89	0.97	0.78
	DLB	1.13	—	1.09	0.88
	FTD	1.05	0.93	—	0.82
	Other	1.28	1.14	1.24	—
<2	AD	—	0.64	0.99	0.93
	DLB	1.55	—	1.55	1.45
	FTD	1.02	0.66	—	0.95
	Other	1.07	0.69	1.06	—
2–4		(Reference)			
	AD	—	0.89	0.97	0.78
	DLB	1.13	—	1.09	0.88
	FTD	1.05	0.93	—	0.82
5+	Other	1.28	1.14	1.24	—
	AD	—	0.64	0.99	0.93
	DLB	1.55	—	1.55	1.45
	FTD	1.02	0.66	—	0.95
No. of other contributing diagnoses	Other	1.07	0.69	1.06	—

Characteristic	Earlier visit diagnosis	Later visit diagnosis			
		AD	DLB	FTD	Other
None		(Reference)			
1	AD	—	3.45	2.19	2.48
	DLB	0.29	—	0.63	0.72
	FTD	0.46	1.57	—	1.13
	Other	0.40	1.39	0.88	—
2+	AD	—	5.79	1.84	5.86
	DLB	0.17	—	0.31	1.01
	FTD	0.55	3.15	—	3.19
	Other	0.17	0.99	0.32	—
Informant		(Reference)			
None		(Reference)			
Spouse/partner	AD	—	0.44	2.06	0.92
	DLB	2.26	—	4.67	2.08
	FTD	0.52	0.23	—	0.47
	Other	1.09	0.48	2.25	—
Other	AD	—	0.39	2.31	0.81
	DLB	2.53	—	5.86	2.05
	FTD	0.46	0.18	—	0.38
	Other	1.23	0.49	2.84	—
Visit transition		(Reference)			
1→2		(Reference)			
2→3	AD	—	1.06	0.77	0.95
	DLB	0.94	—	0.72	0.90
	FTD	1.30	1.38	—	1.24
	Other	1.05	1.11	0.81	—
3→4	AD	—	0.95	1.00	0.77
	DLB	1.05	—	1.05	0.81
	FTD	1.00	0.95	—	0.77
	Other	1.30	1.24	1.30	—
4→5	AD	—	2.72	1.75	1.08

Characteristic	Earlier visit	Later visit diagnosis			
	diagnosis	AD	DLB	FTD	Other
	DLB	0.37	—	0.64	0.39
	FTD	0.57	1.59	—	0.62
	Other	0.93	2.52	1.61	—

Primary Clinical Etiologic Diagnosis on Visits 1 and 2 in Relation to Primary Neuropathological Diagnosis among 526 Decedents with Brain Autopsy

Table 5

Clinical diagnosis	Primary Neuropathological Diagnosis				
	AD	DLB	VaD	FTLD	Hippocampal sclerosis
On Visit 1:					
AD	301	38	21	19	7
DLB	15	29	0	4	0
VaD	4	1	4	0	0
FTD	6	1	0	22	0
PPA	5	1	1	9	0
PD	1	9	0	0	0
Other	4	1	0	7	0
Undetermined	5	1	0	1	0
On Visit 2:					
AD	301	30	21	22	7
DLB	16	36	0	4	0
VaD	3	2	4	0	0
FTD	7	1	1	17	0
PPA	4	1	0	9	0
PD	1	10	0	0	0
Other	6	1	0	9	0
Undetermined	3	0	0	1	0