

## UTILITY OF THE APOLIPOPROTEIN E GENOTYPE IN THE DIAGNOSIS OF ALZHEIMER'S DISEASE

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### ABSTRACT

**Background** The  $\epsilon 4$  allele of the gene encoding apolipoprotein E (*APOE*) is strongly associated with Alzheimer's disease, but its value in the diagnosis remains uncertain.

**Methods** We reviewed clinical diagnoses and diagnoses obtained at autopsy in 2188 patients referred to 1 of 26 Alzheimer's disease centers for evaluation of dementia. The sensitivity and specificity of the clinical diagnosis or the presence of an *APOE*  $\epsilon 4$  allele were calculated, with pathologically confirmed Alzheimer's disease used as the standard. The added value of the *APOE* genotype was estimated with pretest and post-test probabilities from multivariate analyses to generate receiver-operating-characteristic curves plotting sensitivity against the false positive rate.

**Results** Of the 2188 patients, 1833 were given a clinical diagnosis of Alzheimer's disease, and the diagnosis was confirmed pathologically in 1770 patients at autopsy. Sixty-two percent of patients with clinically diagnosed Alzheimer's disease, as compared with 65 percent of those with pathologically confirmed Alzheimer's disease, had at least one *APOE*  $\epsilon 4$  allele. The sensitivity of the clinical diagnosis was 93 percent, and the specificity was 55 percent, whereas the sensitivity and specificity of the *APOE*  $\epsilon 4$  allele were 65 and 68 percent, respectively. The addition of information about the *APOE* genotype increased the overall specificity to 84 percent in patients who met the clinical criteria for Alzheimer's disease, although the sensitivity decreased. The improvement in specificity remained statistically significant in the multivariate analysis after adjustment for differences in age, clinical diagnosis, sex, and center.

**Conclusions** *APOE* genotyping does not provide sufficient sensitivity or specificity to be used alone as a diagnostic test for Alzheimer's disease, but when used in combination with clinical criteria, it improves the specificity of the diagnosis. (N Engl J Med 1998; 338:506-11.)

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FOR the clinical diagnosis of Alzheimer's disease, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) Work Group,<sup>1</sup> which include recommended laboratory and brain-imaging studies, have excellent reliability<sup>2-4</sup> and validity.<sup>5-8</sup> The presence in a patient with dementia of one or more  $\epsilon 4$  alleles of the gene for apolipoprotein E (*APOE*  $\epsilon 4$ ), as compared with the  $\epsilon 3$  and  $\epsilon 2$  alleles, has consistently been associated with Alzheimer's disease.<sup>9-11</sup> In a few small postmortem studies of the *APOE* genotype in the clinical diagnosis of Alzheimer's disease, the sensitivity of the *APOE*  $\epsilon 4$  allele ranged from 46 to 78 percent, whereas the specificity was nearly 100 percent.<sup>12,13</sup> Two additional studies raised doubts about the value of the *APOE* genotype in the diagnosis, but neither included postmortem confirmation.<sup>14,15</sup>

To evaluate the usefulness of the *APOE* genotype in the diagnosis of Alzheimer's disease among persons with dementia, we pooled data from 26 Alzheimer's disease centers in the United States for patients with pathological diagnoses of dementia of various causes in whom *APOE* genotypes were determined. Using the pathological diagnosis of Alzheimer's disease as the standard, we compared the sensitivity and specificity of the clinical diagnosis of Alzheimer's disease, the *APOE* genotype, and the clinical diagnosis and *APOE* genotype determined sequentially.

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\*Other participating investigators and institutions are listed in the Appendix.

## METHODS

## Subjects

We reviewed the clinical diagnoses and diagnoses obtained at autopsy in 3177 patients referred to 26 Alzheimer's disease centers for evaluation of dementia. The demographic variables recorded included age at the time of the clinical diagnosis of dementia, age at death, sex, and ethnic group.<sup>16</sup> All clinical and pathological diagnoses were made without knowledge of the *APOE* genotype. Each center had obtained approval for the investigation from its institutional review board.

The NINCDS-ADRDA criteria,<sup>1</sup> the criteria of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III)<sup>17</sup> and the third edition, revised (DSM-III-R),<sup>18</sup> or the criteria of Cummings and Benson,<sup>19</sup> which are similar to one another, were used for the clinical diagnosis of Alzheimer's disease. These criteria are based on clinical, biochemical, and radiologic examinations. The criteria for the clinical diagnosis of vascular dementia, which were also similar, were those recommended by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences<sup>20</sup> or by Chui et al.<sup>21</sup> For Parkinson's disease, the criteria of Hughes et al.<sup>22</sup> were used in combination with those of DSM-III<sup>17</sup> or DSM-III-R.<sup>18</sup>

## Neuropathological Diagnosis

The primary and secondary neuropathological diagnoses included definite, probable, and possible Alzheimer's disease; definite Parkinson's disease; changes related to Parkinson's disease; cerebrovascular disease; Pick's disease; lobar atrophy without Pick's bodies; and other diseases. At most centers the diagnoses were based on the standardized neuropathological criteria from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).<sup>23</sup> Some centers used the Khachaturian<sup>24</sup> criteria for the diagnosis of Alzheimer's disease, which are similar to the CERAD criteria. If neither were used, center investigators specified how the postmortem diagnosis was made.

*APOE* Genotype

The *APOE* genotypes of genomic DNA from blood or other tissues were determined at each center according to a standard protocol in which the DNA was amplified by the polymerase chain reaction (PCR) as described by Hixson and Vernier.<sup>25</sup> Crude DNA extracts from paraffin-embedded sections were prepared as described by De Souza et al.<sup>26</sup> and used for the *APOE* restriction-fragment-isotyping reactions<sup>9</sup> in a single laboratory at Duke University. Samples that could not be genotyped by this method were retested with a second *APOE*-genotyping PCR protocol that amplifies the two allele-specific *HhaI* restriction sites separately.<sup>12</sup> Frozen tissues were processed and genotyped as previously described.<sup>9</sup>

## Statistical Analysis

Clinical diagnoses were categorized either as probable or possible Alzheimer's disease<sup>1</sup> or as other types of dementia. Pathological diagnoses were categorized as Alzheimer's disease or other causes of dementia. The pathological definition of Alzheimer's disease included definite, probable, or possible Alzheimer's disease as the primary diagnosis<sup>23,24</sup> and definite or probable Alzheimer's disease<sup>23</sup> as the secondary diagnosis. Patients with the Lewy-body variant of Alzheimer's disease<sup>27</sup> were considered to have Alzheimer's disease, whereas those with the diagnosis of diffuse Lewy-body disease<sup>28</sup> were categorized as having other types of dementia.

The clinical diagnosis of Alzheimer's disease and the presence of an *APOE*  $\epsilon 4$  allele were used as tests in two-by-two contingency tables to determine the sensitivity (the proportion of patients with pathologically confirmed Alzheimer's disease who met the clinical criteria for Alzheimer's disease or who had an *APOE*  $\epsilon 4$

allele) and the specificity (the proportion of patients with other dementias who did not meet the clinical criteria for Alzheimer's disease or who did not have an *APOE*  $\epsilon 4$  allele).<sup>29</sup> We also calculated the overall sensitivity and specificity when the clinical criteria and the *APOE* genotype were used in sequence by first identifying patients with probable or possible Alzheimer's disease on the basis of clinical criteria and then applying the results of *APOE* genotyping.<sup>30</sup>

We used a mixed-effects logistic-regression model,<sup>31</sup> with a random-effects term<sup>32,33</sup> for the contributing centers and fixed-effects terms for age, sex, and each clinical diagnosis, to estimate the pretest probability of pathologically confirmed Alzheimer's disease. We estimated post-test probabilities for each patient by adding a fixed-effect term for the *APOE* genotype. The models were used to generate receiver-operating-characteristic curves<sup>34</sup> plotting the sensitivity against the false positive rate (or 1 - specificity) at 12 arbitrary cutoff points, from 0.1 to 0.975. These cutoff points represented the distribution of probabilities for the pathological diagnosis of Alzheimer's disease on the basis of the clinical diagnosis adjusted for age, sex, racial or ethnic group, and center, first without and then with the *APOE* genotype. Areas under these curves were compared,<sup>35</sup> and the differences were calculated with 99 percent confidence intervals.

## RESULTS

Although data on 3177 patients were reviewed for eligibility, no clinical diagnosis was available for 252 (8 percent) and no pathological diagnosis was available for 143 (5 percent). In the remaining 2782 patients, *APOE* genotypes were available for 1850 (66 percent), and an additional 338 *APOE* genotypes were determined from analysis of frozen or fixed tissue, yielding complete information on 2188 of 3177 patients (69 percent).

There were 1108 (51 percent) women and 1080 men; 97 percent were white, 2 percent were black, and 1 percent were from other racial or ethnic groups. The mean ( $\pm$ SD) age at the time of clinical diagnosis was  $72 \pm 10$  years, and the mean age at death was  $77 \pm 10$  years. These characteristics did not differ significantly from those of the 594 patients for whom *APOE* genotypes were unavailable.

NINCDS-ADRDA criteria<sup>1</sup> were used for the clinical diagnosis of Alzheimer's disease in 78 percent of the patients, DSM-III or DSM-III-R criteria<sup>17,18</sup> in 3 percent, and other standardized criteria in 3 percent. The criteria used were not specified for the remaining 355 patients (16 percent). CERAD neuropathological criteria<sup>23</sup> for various forms of dementia were used in 62 percent, and Khachaturian criteria<sup>24</sup> for the diagnosis of Alzheimer's disease were used in 31 percent. Other criteria for dementia were used in a small number of patients (6 percent). The pathological criteria used were not specified for 28 patients (1 percent).

The sensitivity of the clinical diagnosis of Alzheimer's disease was 93 percent, and the specificity was 55 percent (Table 1). Stratifying according to the type of clinical or pathological criteria used or the sex of the patient did not significantly change these values. The specificity, but not the sensitivity, varied significantly according to age ( $P < 0.001$ ). For exam-

**TABLE 1.** CORRESPONDENCE BETWEEN THE CLINICAL DIAGNOSIS AND THE PATHOLOGICAL DIAGNOSIS IN 2188 PATIENTS WITH DEMENTIA.\*

| CLINICAL DIAGNOSIS      | PATHOLOGICAL DIAGNOSIS |                          |
|-------------------------|------------------------|--------------------------|
|                         | ALZHEIMER'S DISEASE    | OTHER CAUSES OF DEMENTIA |
|                         | no. of patients        |                          |
| Alzheimer's disease     | 1643                   | 190                      |
| Other types of dementia | 127                    | 228                      |
| Total                   | 1770                   | 418                      |

\*The sensitivity of the clinical diagnosis of Alzheimer's disease used as a diagnostic test was 93 percent (1643 ÷ 1770; 95 percent confidence interval, 92 to 94 percent), and the specificity was 55 percent (228 ÷ 418; 95 percent confidence interval, 50 to 59 percent).

**TABLE 2.** CORRESPONDENCE BETWEEN THE PRESENCE OF THE *APOE*  $\epsilon 4$  ALLELE AND THE PATHOLOGICAL DIAGNOSIS OF ALZHEIMER'S DISEASE IN 2188 PATIENTS WITH DEMENTIA.\*

| <i>APOE</i> GENOTYPE    | PATHOLOGICAL DIAGNOSIS |                          |
|-------------------------|------------------------|--------------------------|
|                         | ALZHEIMER'S DISEASE    | OTHER CAUSES OF DEMENTIA |
|                         | no. of patients        |                          |
| ≥1 $\epsilon 4$ alleles | 1142                   | 133                      |
| No $\epsilon 4$ alleles | 628                    | 285                      |
| Total                   | 1770                   | 418                      |

\*The sensitivity of the presence of an *APOE*  $\epsilon 4$  allele used as a diagnostic test for Alzheimer's disease was 65 percent (1142 ÷ 1770; 95 percent confidence interval, 62 to 67 percent), and the specificity was 68 percent (285 ÷ 418; 95 percent confidence interval, 64 to 73 percent).

ple, in patients less than 66 years of age (the first quartile), the specificity of the clinical diagnosis was 66 percent and the sensitivity was 93 percent, whereas among those over the age of 79 years (the fourth quartile), the specificity was 23 percent and the sensitivity was 94 percent. Among whites, the sensitivity was slightly higher and the specificity was lower ( $P < 0.01$ ) than in patients from other racial or ethnic groups, but nonwhites represented only 3 percent of the patients. There were no significant differences between the centers.

The presence of one or more *APOE*  $\epsilon 4$  alleles as a test for the pathological diagnosis of Alzheimer's disease had a sensitivity of 65 percent and a specificity of 68 percent (Table 2). These results were similar among quartiles of age, between sexes, and among racial or ethnic groups, but there were slight differences between centers ( $P = 0.04$ ). When the presence of the *APOE*  $\epsilon 4/\epsilon 4$  genotype was considered a positive test result, the sensitivity fell to 14 percent, but the specificity increased to 95 percent.

The sensitivity and specificity for the clinical diagnosis did not change significantly when they were recalculated with stratification according to the individual *APOE* genotypes (Table 3). Though the specificity among patients with the *APOE*  $\epsilon 2/\epsilon 2$  genotype was higher than in other genotype groups, this group included only nine patients.

For the sequential testing procedure, the 1833 patients who met the clinical criteria for Alzheimer's disease were identified and then the results of *APOE* genotyping were added. The presence of one or more *APOE*  $\epsilon 4$  alleles decreased the sensitivity to 61 percent but increased the specificity to 84 percent (Table 4).

Among the 1142 patients who met the clinical criteria for Alzheimer's disease and had an *APOE*  $\epsilon 4$  al-

**TABLE 3.** SENSITIVITY AND SPECIFICITY OF THE CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE ACCORDING TO THE *APOE* GENOTYPE.\*

| <i>APOE</i> GENOTYPE    | BOTH CLINICAL AND PATHOLOGICAL CRITERIA FOR AD | ONLY CLINICAL CRITERIA FOR AD | ONLY PATHOLOGICAL CRITERIA FOR AD | NEITHER CLINICAL NOR PATHOLOGICAL CRITERIA FOR AD | SENSITIVITY | SPECIFICITY |
|-------------------------|--|-------------------------------|-----------------------------------|---|-------------|-------------|
|                         |  |                               |                                   |   |             |             |
| $\epsilon 4/\epsilon 4$ | 227  | 17                            | 14                                | 9   | 93          | 39          |
| $\epsilon 4/\epsilon 3$ | 795  | 47                            | 49                                | 54  | 94          | 52          |
| $\epsilon 4/\epsilon 2$ | 54   | 2                             | 3                                 | 4   | 96          | 57          |
| $\epsilon 2/\epsilon 2$ | 4  | 0                             | 1                                 | 4   | 100         | 80          |
| $\epsilon 2/\epsilon 3$ | 55   | 5                             | 17                                | 20  | 92          | 54          |
| $\epsilon 3/\epsilon 3$ | 508  | 56                            | 106                               | 137   | 90          | 56          |
| Total                   | 1643   | 127                           | 190                               | 228   | 93          | 55          |

\*AD denotes Alzheimer's disease.

lele, 66 (6 percent) had pathological diagnoses other than Alzheimer's disease — specifically, Parkinson's disease or changes related to Parkinson's disease (18 patients), cerebrovascular disease (14 patients), Pick's disease or other frontotemporal dementia (8 patients), no distinct brain abnormalities (8 patients), diffuse Lewy-body disease (5 patients), progressive subcortical gliosis (3 patients), striatonigral degeneration (2 patients), hippocampal sclerosis (2 patients), dementia associated with argyrophilic grains (2 patients), and multiple sclerosis, multisystem atrophy, normal-pressure hydrocephalus, and amyloid angiopathy with chronic meningitis (1 patient each).

Receiver-operating-characteristic curves indicated that adding information on the *APOE* genotype to the clinical diagnosis reduced the false positive rate (Fig. 1). The areas under the curve were 0.80 for the age-adjusted *APOE* genotype alone, 0.84 for the multivariate-adjusted clinical diagnosis of Alzheimer's disease, and 0.87 for the multivariate-adjusted clinical diagnosis plus the *APOE* genotype. The differences between the areas under the curves<sup>36</sup> representing the age-adjusted *APOE* genotype and the clinical diagnosis with the *APOE* genotype and the clinical diagnosis without it were significant (*APOE* genotype alone vs. clinical diagnosis alone, 4 percent; 99 percent confidence interval, 1 to 8 percent; and *APOE* genotype alone vs. *APOE* genotype combined with the clinical diagnosis, 8 percent; 99 percent confidence interval, 5 to 10 percent). Most important, the difference in the areas under the curves for the clinical diagnosis with the *APOE* genotype and the clinical diagnosis without it was significant (4 percent; 99 percent confidence interval, 2 to 6 percent;  $P < 0.001$ ).

## DISCUSSION

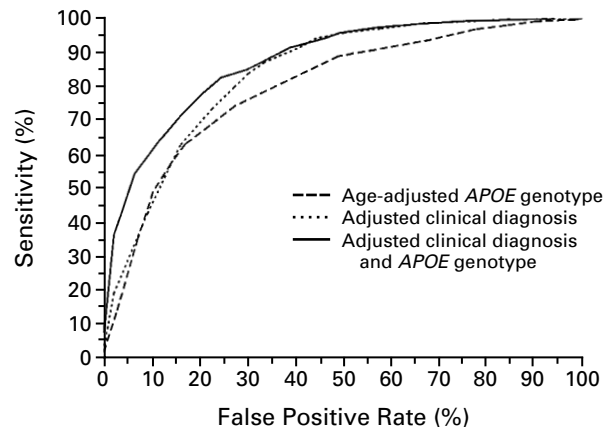
The presence of the *APOE*  $\epsilon 4$  allele has been regarded as a risk factor for sporadic and familial late-onset Alzheimer's disease,<sup>9-11,37-39</sup> a measure of genetic susceptibility to Alzheimer's disease,<sup>40-42</sup> and an adjunct to NINCDS-ADRDA criteria for the diagnosis of probable Alzheimer's disease.<sup>12,42</sup> *APOE* genotyping has also been examined as a potential diagnostic test for Alzheimer's disease.<sup>12-16</sup> We found that clinical criteria for the diagnosis of Alzheimer's disease were highly sensitive, but their specificity was low, resulting in a high false positive rate. These values did not change when stratified according to individual *APOE* genotypes, contrary to previous reports.<sup>12,13</sup> However, sequential use of the *APOE* genotype with the clinical criteria for Alzheimer's disease significantly improved the specificity of the clinical diagnosis, reducing the false positive rate but also decreasing the sensitivity. This finding implies that *APOE* genotyping might be reserved for patients who meet the clinical criteria for Alzheimer's disease.

The sequential use of diagnostic tests as described

**TABLE 4.** SEQUENTIAL USE OF *APOE* GENOTYPING AMONG 1833 PATIENTS WHO MET THE CLINICAL CRITERIA FOR ALZHEIMER'S DISEASE.\*

| <i>APOE</i> GENOTYPE        | PATHOLOGICAL DIAGNOSIS |                          |
|-----------------------------|------------------------|--------------------------|
|                             | ALZHEIMER'S DISEASE    | OTHER CAUSES OF DEMENTIA |
| $\geq 1 \epsilon 4$ alleles | 1076                   | 66                       |
| No $\epsilon 4$ alleles     | 567                    | 124                      |
| Total                       | 1643                   | 190                      |

\*The net sensitivity was determined by dividing the number of patients who met the clinical criteria for Alzheimer's disease and had an *APOE*  $\epsilon 4$  allele ( $n = 1076$ ) by the total number of patients with pathologically confirmed Alzheimer's disease ( $n = 1770$ ) ( $1076 \div 1770 = 61$  percent). The net specificity was determined by dividing the number of patients who did not meet the clinical or pathological criteria for Alzheimer's disease ( $n = 228$ ) plus those without pathologically confirmed Alzheimer's disease or an *APOE*  $\epsilon 4$  allele ( $n = 124$ ) by the total number of patients with pathological diagnoses other than Alzheimer's disease ( $n = 418$ ) ( $352 \div 418 = 84$  percent).



**Figure 1.** Receiver-Operating-Characteristic Curves for the Age-Adjusted *APOE* Genotype Alone; the Clinical Diagnosis Adjusted for Age, Sex, and Center; and the Adjusted Clinical Diagnosis plus the *APOE* Genotype.

The area under the curve was 0.80 for the age-adjusted *APOE* genotype, 0.84 for the multivariate-adjusted clinical diagnosis, and 0.87 for the multivariate-adjusted clinical diagnosis combined with the *APOE* genotype. The differences between the areas under the curve<sup>36</sup> representing the age-adjusted *APOE* genotype and the clinical diagnosis with the *APOE* genotype and the clinical diagnosis without it were significant.

in this study usually increases specificity while decreasing sensitivity, because the second diagnostic test is only used in those who test positive with the first test.<sup>30</sup> The false positive rate typically decreases or does not change, because the second test only identifies patients who do not have disease (a true negative result). The second test does not increase the detection of additional cases that were missed by the first test.

Receiver-operating-characteristic analysis confirmed the added value of information on the *APOE* genotype combined with the multivariate-adjusted clinical diagnosis, although the increase was smaller than that calculated with the two-by-two contingency tables. The two-by-two contingency tables limit the prior probability to a single proportion based on the total number of patients with pathologically confirmed Alzheimer's disease. The multivariate models allowed us to determine the specific contributions of *APOE* genotyping to the clinical diagnosis over a range of prior probabilities.

Consensus statements<sup>40,41</sup> and reviews<sup>42,43</sup> of the topic have generally concluded that the value of *APOE* genotyping for the clinical diagnosis of Alzheimer's disease has not been firmly established. The results of our study provide an indication of the way in which *APOE* genotyping might be used in patients with a clinical diagnosis of Alzheimer's disease. We did not investigate whether *APOE* genotyping should replace any of the currently recommended laboratory procedures, such as brain imaging or psychological testing, nor did we address the stage of illness at which genotyping might be most useful.

The 66 patients who met clinical criteria for Alzheimer's disease and had an *APOE*  $\epsilon 4$  allele but did not have confirmation of the disease at postmortem examination deserve further scrutiny because the disorders identified in these patients have been found in patients both with and without Alzheimer's disease at postmortem examination.

The study was limited by the lack of access to the test results of individual laboratories used to establish the criterion-based clinical diagnoses. Other than cognitive testing or formal neuropsychological evaluations, these tests, which include brain imaging and blood tests (e.g., liver and renal function, thyroid function, and complete blood count), are done primarily to identify other forms of dementia. The added value of any new test for Alzheimer's disease will need to be evaluated with currently recommended laboratory and diagnostic tests.

The patients whose data were used in this study were probably not typical of those encountered in many health care systems. Rather, they were representative of patients with dementia who were referred for medical evaluation or care at a specialized research center focused on Alzheimer's disease. Whether the clinical criteria and the *APOE* geno-

type would provide similar levels of sensitivity and specificity in more typical clinical settings needs to be determined. We do not know whether our results extend to blacks or patients of other racial or ethnic backgrounds because few of them were studied.

The proliferation of diagnostic tests for Alzheimer's disease implies that greater precision in the diagnosis is needed. *APOE* genotyping can improve the specificity of the clinical diagnosis of Alzheimer's disease, but it cannot be used to provide absolute confirmation. If the routine evaluation of patients with dementia includes genetic tests such as *APOE* genotyping, consideration of the implications for families of patients with a "positive" test result will be required.

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A patent on the use of *APOE* genotyping for the diagnosis of Alzheimer's disease has been issued to Duke University Medical Center. This patent has been licensed by Athena Neurosciences for use in diagnosis in patients with cognitive impairment.

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## APPENDIX

The following investigators and Alzheimer's disease centers also participated in the study: *Baylor College of Medicine*: S. Appel, R. Doody, J. Kirkpatrick, J. Li; *Case Western Reserve University*: P. Whitehouse, D. Geldmacher, J. Stuckey; *Columbia University*: M. Shelanski, J. Goldman, B. Tycko; *Duke University Medical Center*: M. Pericak-Vance, C. Hulette; *Emory University*: M. Gearing, H. Kim; *Harvard Medical School*: J. Growdon, D. Reardon, T. Hedley-Whyte; *Indiana University*: B. Ghetti, M. Farlow, H. Hendrie, F. Unverzagt; *Johns Hopkins University*: D. Price, C. Kawas; *Mayo Clinic*: R. Petersen, S. Waring, J. Parisi, S. Thibodeau; *Mount Sinai School of Medicine*: K. Davis, D. Marin, H. Haroutunian, D. Greenberg; *New York University*: S. Ferris, B. Quinn, B. Reisberg, M. de Leon; *Oregon Health Sciences University*: J. Kaye, G. Murdoch, M. Ball; *Rush-Presbyterian-St. Luke's*: D. Bennett, E. Cochran; *University of California-Davis*: W. Jagust, B. Reed, W. Ellis; *University of California-Los Angeles*: H. Vinters, J. Cummings; *University of California-San Diego*: L. Thal, R. Katzman, D. Galasko, M. Sundsmo; *University of Kansas*: W. Koller, K. Lyons; *University of Kentucky*: W. Markesbery, D. Wekstein, M. Kindy; *University of Michigan*: S. Gilman, N. Foster, R. Albin, A. Sima, J. Fink; *University of Pennsylvania*: J. Trojanowski, C. Clark; *University of Pittsburgh*: S. DeKosky, M. Kamboh, R. Ferrell; *University of Rochester*: P. Coleman, D. Ryan; *University of California-Irvine*: C. Finch, J. Buckwalter, C. Miller; *University of Texas Southwestern Medical Center*: R. Rosenber, C. White III, M. Weiner; *University of Washington-Seattle*: M. Raskind, E. Peskind, J. Leverenz, D. Nochlin; *Washington University Medical Center*: J. Morris, E. Grant, A. Goate.

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**CORRECTION**

**Utility of the Apolipoprotein E Genotype in the  
Diagnosis of Alzheimer's Disease**

Utility of the Apolipoprotein E Genotype in the Diagnosis of Alzheimer's Disease . On page 508, in Table 3, the column headings for columns 3 and 4 ("Only Clinical Criteria for AD" and "Only Pathological Criteria for AD") should have been reversed.