



9650 Rockville Pike  
Bethesda, MD 20814-3998  
Telephone 301-634-7127  
Fax 301-634-7275  
E-mail [acmg@acmg.net](mailto:acmg@acmg.net)

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From the American College of Medical Genetics, Bethesda, MD.

A complete list of the American College of Medical Genetics/American Society of Human Genetics (ACMG/ASHG) Working Group on ApoE and Alzheimer Disease appears at the end of this article.

This statement is endorsed by the American College of Medical Genetics, the American Society of Human Genetics, the American Academy of Neurology, the American Psychiatric Association, and the National Institutes of Health-Department of Education Working Group on Ethical, Legal, and Social Implications of Human Genome Research

Corresponding author: Lindsay Farrer, PhD, Department of Neurology, Boston University School of Medicine, 80 E Concord St, Boston, MA 02118-2394

### CONSENSUS STATEMENT

#### Statement on Use of Apolipoprotein E Testing for Alzheimer Disease

**American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer Disease**

**Objective.** To evaluate the published data on the association between apolipoprotein E genotype (*APOE*) and Alzheimer disease (AD) and determine whether the data support the use of genetic testing for diagnosis or prediction of disease. This statement is intended for neurologists, psychiatrists, geneticists, primary care providers, diagnostic laboratories, and the public.

**Participants.** The joint American College of Medical Genetics (ACMG) and American Society of Human Genetics (ASHG) Test and Technology Transfer Committee developed a 10-member ACMG/ASHG Working Group to assess available data on the association of AD with *APOE* alleles. To ensure inclusion of clinical specialists primarily involved with AD patients and families, the American Academy of Neurology (AAN) and the American Psychiatric Association (APA) appointed liaisons to the Working Group.

**Evidence.** Peer-reviewed journal publications obtained from an *Index Medicus* search or known to members of the Working Group were the source of data on which the statement is based.

**Consensus Process.** Following discussions with all members of the Working Group, a draft statement was prepared by the chair and circulated among all members until a consensus was reached. The consensus draft was sequentially reviewed and endorsed by the appropriate scientific and executive committees of the ACMG, ASHG, AAN, APA, and the National Institutes of Health-Department of Education Working Group on Ethical, Legal, and Social Implications of Human Genome Research. In some instances, suggestions from these committees were incorporated into the final statement.

**Conclusions.** There is general consensus that *APOE* epsilon-4 is strongly associated with AD and that when present may represent an important risk factor for the disease. However, at the present time it is not recommended for use in routine clinical diagnosis nor should it be used for predictive testing. Studies to date indicate that the *APOE* genotype alone does not provide sufficient sensitivity or specificity to allow genotyping to be used as a diagnostic test. Because AD develops in the absence of *APOE* epsilon-4 and because many with *APOE* epsilon-4 seem to escape disease, genotyping is also not recommended for use as a predictive genetic test. The results of a collaborative study under way will clarify some of these issues. Whether *APOE* genotypes have other uses in the management of AD will become apparent over the next few years.

(*JAMA*. 1995;274:1627-1629)

RECENT ADVANCES in the genetics of Alzheimer disease (AD) have raised the possibility of widespread DNA testing for diagnosis and prediction of AD. At least several academic laboratories and private companies are offering the apolipoprotein E genotype (*APOE*) polymerase chain reaction assay as a "genetic test" for AD. At the present time, the antemortem diagnosis of AD is based on (1) progressive worsening over several months in memory and other cognitive functions verified by neuropsychological tests and (2) the demonstrated absence of diseases (eg, vascular dementia, vitamin B-12 deficiency, hypothyroidism, alcohol-induced dementia, brain tumor, and normal-pressure hydrocephalus) that could produce similar deficits through appropriate laboratory and brain imaging tests.[1,2] Even following an extensive diagnostic workup by AD specialists, which may require repeat evaluations over several years, postmortem studies indicate an incorrect clinical diagnosis in 4% to 35% of cases.[3-5] While genetic tests may help resolve a diagnosis and reduce diagnosis-related costs, several important questions must be addressed before widespread *APOE* testing can be recommended.

## BACKGROUND

Apolipoprotein E is a plasma protein involved in the transport of cholesterol and other hydrophobic molecules and is encoded by a gene on chromosome 19.[6] Certain forms of apolipoprotein E have been linked to disorders of cholesterol metabolism and coronary heart disease.[7] A competing association between risk of AD and the *APOE* gene has been demonstrated. It appears that 34% to 65% of individuals with AD carry the *APOE* epsilon-4 allele, while it is present in only approximately 24% to 31% of the nonaffected adult population. [8-11] The association between AD and *APOE* epsilon-4 has been confirmed in clinic-based and population-based studies of patients from North America, Europe, and Japan.[12] Mounting evidence indicates that disease risk increases and the age of onset decreases with the number of *APOE* epsilon-4 alleles.[13] Moreover, preliminary evidence suggests that the epsilon-2 allele, which is only half as frequent as epsilon-4, may be protective against AD,[14-17] but there is disagreement on this point.[18,19]

## APOE GENETIC TESTING

At the present time, it would be premature to offer *APOE* as a genetic test for AD among either members of high-risk families or the general population. Despite epidemiological and histochemical evidence implicating the epsilon-4 allele as a genetic risk factor for AD, a number of critical questions must be answered to assess the validity of such testing in both diagnostic and predictive situations. These questions and what is thought to be the best information regarding them include, but are not limited to, the following.

### What Is the Predictive Value of *APOE* Testing for AD?

The presence of an epsilon-4 allele is not necessary for the development of AD.[20] At least 35% to 50% of persons with AD do not carry an epsilon-4 allele, and some may have other genetic or nongenetic defects for which there currently are no tests. Genotypes of epsilon-2/epsilon-3 or epsilon-3/epsilon-3 could be falsely reassuring. Although some early reports based on data from families and institutionalized subjects implied that nearly all epsilon-4/epsilon-4 homozygotes who reach 80 years of age will develop AD,[13,21] population-based studies raise questions about the strength of this association.[9,22] Furthermore, between 26% and 50% of epsilon-4 heterozygotes, who account for 88% of persons having at least one epsilon-4 allele, will develop AD.[9,13] The epsilon-4 allele has moderate specificity for AD, with estimates ranging from 0.75 to 0.81.[9,23] *APOE* status is a strong predictor of patients' ultimate outcome once they have been designated as having a memory impairment, but the correlation is not perfect. [24] Therefore, a test result showing an individual has one or even two epsilon-4 alleles might create undue anguish and worry. Despite clarification of issues related to clinical validation,[20] information concerning the predictive value of the epsilon-4 allele for AD from some laboratories currently marketing the *APOE* test is being misinterpreted. It is important to distinguish between *APOE* and other AD susceptibility loci, including the beta-amyloid precursor protein gene (*APP*) on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1. [25-27] Whereas mutations in *APP*, presenilin 1, or presenilin 2 are deterministic (ie, individuals possessing such defects are certain to develop AD unless they die prematurely from other causes), evidence to date suggests that the *APOE* genotype is not.

### What is the Specificity of the epsilon-4 Allele for AD vs Other Dementias?

Several studies suggest that the epsilon-4 allele is also present in greater frequency in persons with Lewy body disease and Pick disease.[28-33] It is unclear from the literature, however, whether epsilon-4 is also associated with vascular dementia because the sample sizes were small and diagnostic criteria are not uniform across studies.[30,34-36]

### Is There a Relevant Quantifiable Protective Effect of the epsilon-2 Allele, and if so, is This Additive to the Effects of Other *APOE* Alleles?

Because estimates of the frequency of epsilon-2 in AD patients and individuals from the general population differ by less than 5%, [9,14-19] a sample of cases and controls, much larger than any of those in any single study,[12-17] must be evaluated before reliable conclusions about the protective effect of the epsilon-2 allele can be made.

### How Are *APOE* Allele Associations Affected By Ethnicity and/or Racial Origin?

Although the frequency of AD is relatively similar in most populations, *APOE* allele frequencies vary significantly in different racial and ethnic groups. The epsilon-4 allele does not appear to be elevated in Swedish AD patients.[37,38] The epsilon-4/AD association in African Americans is controversial [39,40] and may appear weaker perhaps because the frequency of epsilon-4 is higher among individuals of African origin,[41-45] apparently without an increased incidence of AD. Remarkably, epsilon-2 may increase risk for AD in some populations.[19,39]

### Do Other Risk Factors Interact With *APOE*?

If *APOE* is but one of several genetic and environmental factors that influence risk of AD, its presence may or may not be associated with disease because of confounders. The number of epsilon-4 alleles and a family history of a first-degree relative with memory problems influence the risk of AD, but whether these

factors act additively or interactively in the prediction of AD is unclear.[46-48] The influence of APOE genotype on AD risk may also be modulated by cholesterol level, alpha-1 -antichymotrypsin genotype, and very low-density lipoprotein receptor gene,[11,49,50] but these interactions need to be confirmed.

### **Finally, What Are the Risks and Benefits of Predictive Testing for AD, a Late-Life Disorder, Without an Accurate Prediction of Onset Age or the Ability to Affect Its Course?**

Arguably, predictive testing may be valuable only if prevention can be affected by lifestyle changes or early drug intervention.

### **CURRENT STATUS OF DIAGNOSTIC AND PREDICTIVE TESTING**

The use of *APOE* genotyping as a diagnostic test may not be as advantageous or cost-effective as has been suggested.[51] Because most patients presenting to physicians with dementia have AD, the additional information gained by genotyping would be useful only if it reduced the necessity for other more expensive or invasive tests. Individuals homozygous for epsilon-4 are the most likely candidates for disease, but they comprise only 2% to 3% of the general population; even among AD patients, only 15% to 20% have this genotype. Most symptomatic epsilon-4 homozygotes will in fact have AD,[23] but any uncertainty will oblige the physician to exclude other forms of dementia.[52] Moreover, until appropriate studies are performed, the exact sensitivity, specificity, and predictive power of APOE epsilon-4 homozygosity are unclear. [53] With but a single *APOE* epsilon-4 allele, the patient may be more likely to have AD, but not sufficiently to eliminate other components of a diagnostic evaluation including imaging, neuropsychological, and other laboratory tests.[52] If no APOE epsilon-4 allele is present, the patient still requires a full diagnostic workup.[23]

Although the *APOE* genotype might also be used predictively to detect presymptomatic cases, without a practical therapeutic option or the ability to predict age of onset, the benefits of early detection for purposes other than research are not obvious. While family members of some AD patients have requested *APOE* testing for themselves (sometimes for reproductive purposes), the prognostic benefits of the test remain ambiguous. Thus, although *APOE* genotype may be a risk factor for AD, it cannot yet be considered a useful predictive genetic test.[24,51,52] In situations in which predictive testing using *APOE* might be valid, it will be critical to assess the impact of this knowledge on healthy individuals and their relatives. It will become necessary to educate physicians, DNA diagnostic laboratory directors, and the public about the complexities of *APOE* genotyping for AD; to establish safeguards to ensure informed consent; and to ensure that individuals at higher risk will not be subjected to discrimination. A potential concern is the dissemination of *APOE* results obtained in contexts other than AD testing *APOE* genotypes have been determined for many cognitively normal participants of cardiovascular disease research. In accordance with federal regulations regarding the utilization for clinical purposes of genetic data obtained under research protocols (CLIA, 42 CFR Section 493.1992), persons whose *APOE* genotypes were obtained in this manner would be required to provide a new blood sample for evaluation by an accredited diagnostic laboratory in the event that *APOE* testing is warranted for prediction of AD.

Once the questions in this report are answered, *APOE* genotyping may be an important adjunct in some diagnostic and predictive situations. Perhaps a greater utility for *APOE* testing will emerge in evaluating therapeutic options for an individual patient. Genetic factors have been related to course of illness of AD,[54] but the role of *APOE* in survival is controversial.[19,55] Future clinical trials will undoubtedly require patients' *APOE* status for assignment to treatment groups.[23,51]

Coordinated basic and clinical research studies are essential prior to introduction of *APOE* testing into clinical practice. An initiative to examine *APOE* data on patient and control populations for the determination of risks by age, sex, and ethnicity is being launched by the ACMG, and the results will be incorporated in a more comprehensive report of this Working Group. Until more sufficient information is available to address these critical issues, we believe that it is premature to offer DNA diagnostic testing or screening for AD predisposition, outside of carefully monitored research protocols.

*Members of the ACMG/ASHG Working Group on ApoE Testing in Alzheimer Disease include the following: Lindsay A. Farrer, PhD, Boston (Mass) University (chair); Mitchell F. Brin, MD, Mt Sinai Medical Center, New York, NY; Louis Elsas, MD, Emory University, Atlanta, Ca, (ad hoc); Alison Goate, PhD, Washington University, St Louis, Mo; James Kennedy, MD, University of Toronto (Ontario); Richard Mayeux, MD, Columbia University, New York, NY; Richard H. Myers, PhD, Boston (Mass) University; Philip Reilly, MD, JD, Shriver Center, Waltham, Mass; and Neil J. Risch, PhD, Stanford (Calif) University.*

*The Working Group gratefully acknowledges Michael Watson, PhD, for facilitating the development of the final document.*

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