

## Risk Assessment for Alzheimer's Disease with

# *Genetic Susceptibility Testing:* Has the Moment Arrived?

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*F*amily members of patients with Alzheimer's disease (AD) have a higher risk of eventually developing the disease. APOE genotyping is an easily measured genetic variation that could be used to provide a more refined measure of AD risk to those who desire it. However, there are many concerns about whether risk information based upon genetic susceptibility testing can be properly communicated, and whether such information would benefit or harm those receiving it. In this article, these issues are discussed within the framework of what is known to date about AD risk and APOE testing. Empirical data on the benefits and potential harm of genetic susceptibility testing with APOE are currently being collected and studied in the multicenter REVEAL Study (Risk Evaluation and Education for Alzheimer's Disease).

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I wonder, there in the night. What if, one day, I can't remember my son any more than my father could remember me? And what if, one day, my daughter can't remember her father any more than she can remember her own children?<sup>1(p. 213)</sup>

The shared experiences and mutual acknowledgement that bind family members to each other are sorely tested as the persons with Alzheimer's disease (AD) lose memories and eventually even their awareness of the people who love them. This is the sad but familiar agony of families with AD.

An additional burden for some blood relatives of persons with AD is the recognition that they are at an increased risk of developing the disease. This burden is not always evident to clinicians caring for persons with AD.

In cases where the spouse is the caregiver, clinicians may not come in contact with blood relatives. Moreover,

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brothers, sisters, sons, and daughters of persons with AD may dismiss concerns about their own risk as unseemly while the person with AD in their family is living. But these concerns clearly exist and may emerge more fully after the AD patient has died and the deceased person's clinician is no longer involved.

In our clinical care of persons with AD and their families, we have found that many relatives are deeply concerned about their own risk of developing AD and want to understand that risk more fully. Our research over the last 10 years has revealed that simply having a blood relative with AD multiplies the risk of developing AD.<sup>2,3</sup> Now, with the discovery of genetic markers, it has become possible to provide even more specific risk information to family members.<sup>4</sup> As genetic markers for AD are recognized and the risk conferred by specific markers are better understood, the use of genetic susceptibility testing for risk assessment in unaffected individuals has become a practical possibility. Yet many troubling questions remain. How accurate is the most well characterized genetic marker for AD? What are the reasons that people wish to be tested? How will they interpret the information, particularly if it is complex? Will the information be reassuring or frightening to those who seek it, and what sort of discrimination could they face if this information is disclosed to others? How will the development of treatments for preventing AD or slowing disease progression affect the calculus of such questions?

This article describes the current state of knowledge of genetic tests for AD and provides discussion of some practical and ethical issues in this arena.

## GENETIC RISK FACTORS FOR ALZHEIMER'S DISEASE

The genome is the blueprint for life, a double helix of DNA that provides the coding for all biological functions of the organism. Genes are specific regions of the genome that code for proteins, and at the present time, the human genome is estimated to be made up of approximately 30,000 genes. While the function of most genes remains unknown, the pace at which genes and gene products are identified and understood is rapidly accelerating. The coding within each gene varies from person to person. If the gene variation is rare, it is called a mutation. If it is common, it is called a polymorphism.

Several thousand-gene variations are currently known to be associated with diseases. Most of these are not single gene variants that clearly determine whether a person

will or will not develop the disease (deterministic gene variants), but rather are gene variants associated with greater or lesser risk of disease (susceptibility gene variants). The two types of gene variants—deterministic and susceptibility—are each found in Alzheimer's disease. In rare families where AD has an autosomal dominant inheritance pattern and can begin in the 4th or 5th decades of life (less than 2% of families with the disease), deterministic mutations have been found on chromosome 21, chromosome 14, and chromosome 1.<sup>5</sup> If an unaffected person has one of these mutations and lives long enough, he or she will inevitably get the disease.

In common, late-onset AD, the genetic risk factor with the highest attributable risk is not a deterministic mutation, but rather, a susceptibility marker—the apolipoprotein (APOE) polymorphism. Apolipoprotein E is a cholesterol transport protein, and the gene coding for this protein (APOE) on chromosome 19 has 3 co-dominant alleles:  $\epsilon 2/\epsilon 3/\epsilon 4$ , differing by single-base substitutions in the coding region of the gene. Persons with one copy of the  $\epsilon 4$  allele have 3–5 times the risk of developing AD as those who have no copies. Persons with two copies of the  $\epsilon 4$  allele have about 15 times the risk of developing AD. The exact reason for the association between the  $\epsilon 4$  allele and AD is not known, although there are a number of theories involving interaction between APOE and the deposition of destructive forms of amyloid that probably cause AD. There is also evidence that the association between APOE  $\epsilon 4$  and AD may differ in different racial and ethnic groups, although this has not yet been fully settled.<sup>3,4,6</sup> What seems clear is that copies of the  $\epsilon 4$  allele increase the risk of developing AD, and that APOE therefore can be considered a "genetic test" for AD susceptibility.

Is APOE genotyping a "good" genetic test for Alzheimer's disease? As medical tests are judged, APOE genotyping is considered a highly reliable, but not highly accurate, genetic test. This means that the laboratory test for determining the APOE genotype is highly accurate and reproducible when done in a reputable laboratory. However, even when the test correctly reveals the genotype, it does not do a good job of predicting who will get AD. A substantial proportion of  $\epsilon 4$  carriers, including those surviving into the 10th decade, do not become demented; while more than one-third of persons with AD do not have the  $\epsilon 4$  allele.<sup>4</sup> Thus the presence of the APOE  $\epsilon 4$  allele, while describing a genetic variation, should be thought of as a "risk factor" and not as a certain marker of ultimate disease development.



## WHY ARE GENETIC MARKERS OF DISEASE SO SPECIAL?

Why are “genetic risk factors” so special and so difficult to utilize clinically? After all, the whole of clinical medicine involves the implicit and explicit practice of risk assessment. Almost every diagnostic interaction between doctor and patient seeks to determine whether the reported symptoms make one or another disease more or less likely in the doctor’s mind. Is sudden chest pain a heart attack or merely indigestion? If that pain has a crushing quality and radiates down the left arm, a heart attack is more likely. If there is a normal EKG at the same time as the pain, a heart attack is less likely. Clinicians collect information on smoking (historical data), blood pressure (measured in the office), or cholesterol level (through a blood test) to make and communicate judgments on the future likelihood of disease. In clinical discussions with patients, it is understood that a smoking history does not inevitably lead to heart disease, but rather that the risk is substantially greater, and that that risk is mediated by many other factors (known and unknown). Indeed, the well-established role of the physician in our culture is to interpret the symptoms, signs, and risk factors; communicate this interpretation to the patient; and offer whatever treatments are available. The assessment, interpretation, and communication of information between physician and patient does not require that either party be versed in statistics or probabilities, or that there be a cure, or even a treatment, for the disease in question. And, all of this is done (ideally) within a long-term relationship of trust that allows the physician to consider the psychological strengths and weaknesses of the patient.

By contrast, the science of medical genetics is relatively new and the first genetic tests to be applied to human health were largely those that determined whether unborn children were at risk for devastating diseases. These early genetic tests typically informed the decision of a couple to get married with the intention of having children, or the decision of a married couple to have children, or the decision of a pregnant woman to continue that pregnancy. All of these decisions are highly charged and usually involve the psychology of more than one

individual. The risks in some of these situations are precisely known and can be communicated with a sense of accuracy (i.e. “...you have a 50:50 chance of having a child with this disease”). Risk assessment procedures for Mendelian genetic diseases offer more apparent precision than the typical doctor-patient interaction because the potential actions that could be taken as a result of that information (altering plans for marriage, deciding never to have children, terminating a pregnancy) are so dramatic and morally loaded. The specialized vocabulary of the diseases, tests, and statistical risks—along with the need to maintain a nonjudgmental posture around such controversial decisions as termination of pregnancy—led to the development of genetic counseling as a clinical discipline.

But the differences between medical risk assessment and genetic risk assessment go further than the traditions of their practitioners. Genetic markers of disease have a special impact for three reasons. First, genetic markers to date have largely been deterministic, and they have not typically been associated with preventable outcomes, so the psychological concept of “genetics” carries an almost mythical connotation of determinism. Second, there

may be an especially long time delay between the genetic testing and the clinical manifestations of the disease. And third, genetic markers from one individual often give insight into the genetic makeup and health history of other individuals in that person’s family. These special features of genetic markers have led to the well-recognized ethical and psychological concerns and

dangers of genetic testing. These include the possibility of psychological trauma, family discord, and inadvertent transfer of risk information to other family members who do not wish to know it. There is also a growing awareness of the risk of social stigmatization and insurance or employment discrimination.

If one examines APOE genotyping in light of these concerns, one can see that they are all, to some degree, applicable. At the present time, there are modest symptomatic treatments available for patients with AD, but there are no proven treatments to prevent AD or to slow the progression of the disease. Most people who might receive any form of risk assessment for AD would do so many years before the disease would be likely to begin. And, the presence of a single APOE ε4 allele in any family

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member makes it clear to other family members that they are at increased risk of having one as well. In fact, if a parent is known to have two copies of the  $\epsilon 4$  allele, then any knowledgeable offspring of that parent can realize that he or she must have inherited at least one of those copies.

Further, there is potential psychological harm that could result from learning that one has “the Alzheimer’s gene,” particularly if an individual had an inflated sense of the predictive accuracy of the gene, or if that individual really did not want to know. It is also easy to imagine that the presence of an  $\epsilon 4$  allele, and the associated increase in risk of AD, might be cause for employment discrimination or for the denial of health or insurance coverage (particularly long-term care insurance). Thus, there are clear dangers to offering genetic testing for AD with APOE genotyping. However, it should be noted that these dangers remain unmeasured because there have been no well-designed trials to examine the safety of offering such testing.

#### **THE QUESTION OF UTILITY: USEFUL TO WHOM? USEFUL FOR WHAT?**

As described above, there are potential dangers involved in any form of genetic testing. Information, like medication, has “side effects” that are unpredictable in the individual. The question then becomes the same as that which we ask when thinking about prescribing a medication with side effects, i.e., does risk information based upon genetic testing have benefits that justify exposure to the side effects of receiving it?

The most obvious reason to obtain risk assessment for AD would be to select individuals with high risk to receive treatments that might delay or prevent the development of the disease. If such treatments were available, entirely safe, and completely affordable, then the question of risk assessment would be irrelevant. Such a perfect treatment could be “added to the drinking water” to reduce or eliminate AD from the population. So the concept of risk assessment for treatment selection depends upon the assumption that such a treatment not only has been developed, but will be available to some, yet not available to all because of cost or because of significant side effects. At the time of this writing, several treatments such as the AD vaccine and the secretase inhibitors are in clinical trials that might have the ability to delay or prevent AD, but their costs, efficacy, and side effects are not yet established.

Another reason people commonly report that they are interested in obtaining genetic risk assessment for AD is

to better “plan for the future.” When asked what is meant by this, some people report that they wish to know if they are at high risk for AD in order to prepare their finances, to retire early and travel, to purchase long-term care insurance, or to prepare their families for the ravages of the disease. A few people report that they are simply “curious,” and a very few say that they might wish to know in order to plan for suicide if the disease is imminent. Physicians are likely to be less familiar, less comfortable, and, on the whole, less supportive of these reasons because they are not motivated by interventions within the classical medical model. Yet these reasons remain a critical (if unspoken) part of the calculus of current medical screening and treatment decisions. For example, many people are curious about their cholesterol levels, have them measured, and find them to be high, but choose not to take cholesterol-lowering medications. Risk assessment for a medical treatment is likely to be seen as useful to individuals by both themselves and their physicians. In contrast, risk assessment for life planning or curiosity is likely to be seen as useful only to the individual receiving the risk information because these are not issues typically considered by physicians.

#### **THE RIGHT TO KNOW (AND THE RIGHT NOT TO KNOW)**

If risk information is available and desired by an individual, and that information can be communicated in a clear fashion, why should the individual not be able to obtain it? In other words, who has the right to withhold clinically relevant information from individuals, and on what grounds? Precedents in the arena of genetic counseling seem to stress the danger of information, particularly the danger that genetic information could be misunderstood or misinterpreted, leading to harm. By contrast, in general medical practice, where medical (but not genetic) risk information is discussed at every physician-patient encounter, the danger of risk information is expected to be mitigated by the perspective and counsel of the physician—and the risk of misunderstanding is not such an ever-present concern. If people ask physicians about their risk of a particular disease, including their risk based upon blood tests, there is usually no hesitation to discuss this with them.

To date, several expert consensus conferences<sup>7–12</sup> have concluded that genetic risk assessment using APOE should not be provided clinically because the risks of misunderstanding outweigh the potential benefits. Are these positions prudent—or patronizing? When does



protection become unnecessarily paternalistic? The answers to these questions may depend, in part, upon how great the dangers truly are. Yet there have been very few clinical experiences or trials to empirically determine whether receiving genetic susceptibility information is safe or not.

A number of factors would seem relevant to the issue of safety in providing risk assessment for AD with genetic susceptibility testing. First, is the information delivered accurately and in a manner that is understandable, particularly if true understanding relies upon statistical concepts such as probabilities? Trying to explain exactly how much more risk pertains to a person with the APOE ε4 allele is not easy. Simply explaining that a single ε4 allele increases baseline risk “three to five times in comparison to those who do not have the ε4 allele” is not necessarily accurate, because that figure changes depending upon the age of the individual, and is not necessarily informative because people do not know whether their baseline risk is high or low. Using absolute figures such as lifetime cumulative risk may be more accurate but may not be intuitively clear. Thus, the mechanism by which information is conveyed and the skill of the person communicating the risk information are important considerations.

In the case of genotyping for APOE, who might have that knowledge and skill? Is it the personal physician who knows the background of the individual being counseled? Is it the dementia specialist who knows the features of AD? Is it a separate genetic counselor who has been trained in genetics and nondirective communication? While it may not presently be clear who might have all of these skills, the context of the relationship between the person providing the risk assessment information and the person receiving it is probably important. The prior life experience and the family medical history of the person receiving the risk information would likely influence the potential for misunderstanding and even harm. For example, risk information for AD might mean something entirely different to a person with a prominent family history of early cardiac death (a competing risk) than to a person without a strong family history of other

medical conditions. And the psychological impact of AD risk information might be very different for a person who has watched one or more persons suffer from AD in their family than for a person with the same family history who was not a caregiver or close witness to the disease. Even racial or ethnic group identity could be important. Epidemiological studies suggest that in comparison to white Americans, the risk of dementia in African-American family members of AD patients is higher and the risk in Asian American family may be lower.<sup>3,4</sup> An impersonal relationship, or an encounter created solely for the purpose of risk assessment, would seem more vulnerable to miscommunication than an encounter discussing risk assessment that is embedded in a long-term clinical relationship. So, for example, a clinician having a long-term relationship with the individual might better appreciate the strengths and vulnerabilities of the person receiving risk information and could be in a better position to offer clarity or reassurance.

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#### **THE REVEAL STUDY: RISK EVALUATION AND EDUCATION FOR ALZHEIMER'S DISEASE**

The discussion above highlights practical and ethical issues surrounding genetic susceptibility testing, but there are no data about whether it is safe or beneficial to provide genetic susceptibility information through APOE genotyping. While there are a number of factors that we could predict might influence the desire to obtain such testing, and the impact of receiving the results of such testing, we do not yet know if these predictions are correct.

A currently funded study called the REVEAL Study (Risk Evaluation and Education for Alzheimer's Disease) may provide answers to some of these questions. Funded since 1999 by the Ethical, Legal and Social Implications Branch of the National Human Genome Research Institute, this study asks: Who will request susceptibility genotyping with APOE? What will be the psychological benefits and risks of receiving risk assessment in this manner? What real-world decisions (financial, health insurance, or retirement) will be made as a result of receiving susceptibility genotyping for AD risk assess-



ment? The REVEAL Study has so far enrolled over 150 adult children of patients with AD in Boston, Cleveland, and New York City, who have been randomized to receive risk assessment based upon family history and APOE disclosure versus risk assessment based upon family history alone. Results of the REVEAL Study will be available late in 2002.

### USING APOE TO PROVIDE RISK ASSESSMENT FOR AD: HAS THE MOMENT ARRIVED?

The association between APOE genotype and risk of AD has been consistently demonstrated since 1993 and continually refined since then. Yet important questions remain about the nature of this association in different age cohorts, in different ethnic and racial groups, and in conjunction with cardiovascular and cerebrovascular risks. A widespread impression exists that clinical use of APOE genotyping for risk assessment in asymptomatic individuals is not appropriate because a susceptibility genotyping may be incorrectly interpreted, causing psychological harm; because disclosure could be a source of discrimination; and because there are no obvious treatment decisions that would be aided by APOE disclosure. But some of these reasons are changing. The REVEAL Study seeks to show that the probabilistic nature of genetic susceptibility testing for AD can be consistently and clearly communicated and understood. Legislation is in place or proposed at both state and national levels that would help protect against genetic discrimination. Perhaps most important, treatment modalities are in clinical trials that could prevent or delay the onset of AD.

These developments suggest that genetic susceptibility testing for AD (and for other diseases) may have a place in the future clinical lexicon. In order for this to happen rationally, such testing should be examined first in a research context. Just as the Food and Drug Administration certifies clinical trials of new medications for their efficacy and safety, so there should be a regulatory body with clear criteria for measuring and approving the benefits and side effects of predictive tests. As treatments are developed, and the demand for risk assessment increases, such a regulatory body would ensure that scientific evidence on the accuracy and impact of genetic susceptibility testing is used to guide the clinical appropriateness of such testing.

The moment to begin providing APOE genotyping for clinical risk assessment has not yet arrived, since the safety and efficacy of disclosing this information has not been proven. But as research like the REVEAL Study evaluates the impact of such disclosures, and treatments for disease prevention seem likely, that moment is closer than ever, and probably inevitable.

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