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Physicians' propensity to offer genetic testing for Alzheimer's disease: Results from a survey

Gary A. Chase, PhD[1], Gail Geller, PhD[2,3], Suzanne L. Havstad, MA[1], Neil A. Holtzman, MD[3], and Susan Spear Bassett, PhD[4]

Purpose: Examine physician knowledge, preferences, and use of genetic tests for Alzheimer's disease (AD). **Methods:** Survey of 426 community-based physicians treating AD patients. **Results:** Majority gave inaccurate estimates of AD risk. Medical specialty predicted appropriate use of current tests. Recommending substances to prevent memory loss was related to acceptance of error-free tests. High patient loads and familiarity with genetic tests predicted lower tolerance for test error. **Conclusion:** Physicians do not endorse indiscriminate genetic susceptibility testing for AD. However, insufficient knowledge of disease risk, etiology, genetic susceptibility, and use of existing tests indicated a need for further physician education in this area. ***Genet Med*** **2002:4(4):297–303.**

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Alzheimer's disease (AD) is one of the most common threats to the elderly with a risk of approximately 12% to 15% that a 65-year-old would become affected during his or her remaining lifetime; this risk is steeply concentrated toward the end of the lifespan.[1–7] Familial aggregation of disease alters the lifetime risk, with the presence of an affected first-degree relative producing a two- to threefold increase in risk.[8–13]

Initial efforts to understand the role of genetics in AD focused on extremely rare, multigenerational families where disease onset occurs in the fourth or fifth decade of life (early-onset AD). These autosomal dominant forms of the disease account for no more than 5% to 10% of all AD cases. At present, three gene loci are linked to early-onset AD,[14–16] with the presenilin 1 gene on chromosome 14 appearing to be the major early-onset locus.[16] Mutations of these three genes are virtually 100% penetrant in the approximately 100 families studied thus far and explain approximately half of the early-onset cases.[17]

In the vast majority of AD cases, in which disease onset occurs after the age of 65, only the *APOE* gene located on chromosome 19 has been shown to be associated with increased disease risk, with a significantly higher frequency of the ϵ4 allele found in cases compared with controls.[18–21] Although the presence of one ϵ4 allele appears to double the risk of AD at age 65,[1,22,23] a substantial proportion of ϵ4-positive persons never experience the onset of AD. In addition, it appears that roughly 35% to 50% of those suffering from AD do not have the ϵ4 allele, that the frequency of this allele may be similar in other dementing conditions, and that the association of ϵ4 with AD may vary with ethnic background,[24–26] prompting medical geneticists and others to recommend against the use of *APOE* genotyping for prediction of risk in asymptomatic individuals.[24,27]

Continuing advances in molecular genetics will identify other genes that may play a role in AD, further increasing the expectations of the public regarding the predictive accuracy of genetic susceptibility tests and the prospects for effective intervention. Studies indicate the majority of physicians have insufficient training for the understanding of genetic probabilities, penetrance, the notion of competing risk or calculation of positive predictive value.[28,29] A survey of 50 physicians found less than half had accurate knowledge of the baseline risk of AD and <5% understood the alteration in risk associated with the presence of the ϵ4 allele.[1] At the present time, genetic testing for the *APOE* gene as well as the *PS1* gene is available and being marketed directly to physicians for use in appropriate circumstances as defined by the manufacturer.[30] Effective physician patient communication may be hampered by two factors: physician uncertainty regarding the meaning of predictive test results, and physician inability to identify situations for which testing is clearly inappropriate.[29]

This study was undertaken to survey the attitudes and knowledge of physicians regarding probable causes and risk of AD, as well as their propensity to offer genetic testing, both in real testing situations involving the offer of *PS1* and *APOE* and hypothetical scenarios for which only the error rates of the test are to be considered.

SUBJECTS AND METHODS

The physicians included in this study, identified through family informants and medical record review, had evaluated or

From the [1]Department of Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center; and [2]the Bioethics Institute, [3]the Institute of Genetic Medicine, and the [4]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Susan S. Bassett, PhD, Johns Hopkins Hospital, Osler 320, 600 North Wolfe Street, Baltimore, MD 21287-5371.

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treated AD patients enrolled in a genetic linkage study of 165 primarily late-onset families with two or more affected siblings. A total of 520 physicians were initially identified, of which 426 were living and could be located. All were invited to participate, and 171 (40%) responded. These physicians had not previously participated in our ongoing studies. The study was approved for expedited review by the Institutional Review Board, and consent was suggested with return of the survey. The survey was designed as part of a long-term research effort that assesses both physician and patient responses to a number of genetic testing situations. Portions of the questionnaire stemmed from this earlier work.[31,32] The survey was drafted and reviewed by a group which included genetic testing researchers, psychiatrists experienced in Alzheimer's disease treatment, and physicians representing several specialties in a leading university hospital. It was then pilot tested on several university-based physicians who cared regularly for AD patients.

The survey was mailed with a cover letter describing the study, indicating intent, and ensuring confidentiality. The package included an incentive check for $10, as previous work has shown that even small monetary incentives significantly increase physician response rates,[33] and a stamped self-addressed return envelope. Reminder postcards were mailed 3 weeks after the initial mailing.

The survey included, but was not limited to, the following domains:

Physician attributes

These included age, gender, year of residency completion, specialty certification, religious background, influence of religion on decision-making, marital status, and whether AD was present in a parent, grandparent, sibling, spouse, or other relative.

Practice characteristics

Physicians were queried regarding their practice setting, approximate number of total patients under their care, the proportion who reside in nursing homes, experience with AD patients, and their recommendation of drugs or other substances for the possible prevention of memory loss.

Endorsement of causal factors

Physicians were asked to indicate their agreement or disagreement with a list of 13 separate causal factors for AD including chance and inheritance of specific genes.

Knowledge of AD risk

Physicians were asked to supply their estimate of the population risk for AD, the change in risk associated with the presence of an affected parent, and the change in risk associated with a positive test for *APOE* or *PS1*.

Use of currently available AD genetic tests

Physicians were presented with five questions to gauge their familiarity with both the *APOE* and *PS1* tests. A Likert-type scale was constructed from these items for each test, creating familiarity dimensions with Cronbach's alpha (*PS1,* 0.6478; *APOE,* 0.7174) and subsequently dichotomized for use in multiple regression models. In addition, they were presented clinical histories and asked to indicate how likely they would be to offer the *APOE* and *PS1* test to these individuals.

Projected offering of hypothetical genetic tests

Physicians were asked to indicate the minimum positive predictive value (the proportion of patients testing positive who actually develop the disease, PPV) that a genetic test for AD should achieve in order for that test to be offered in practice. They were then presented with questions portraying a range of genetic testing situations (e.g., a perfect test, tests with varying degrees of false negatives, and tests with varying degrees of false positives) and asked whether they would or would not offer the test to their patients.

RESULTS

Physician characteristics, attitudes, and beliefs about AD

The 171 physicians who completed the survey (40% of the sample) had a mean age of 51.7 years (SD = 10.0), were largely male (90.0%) and married (89.4%). Thirty-seven percent indicated that a relative was affected with AD. Their religious background was predominantly Judeo-Christian (35.3% Protestant, 25.9% Jewish, 24.0% Catholic) and 65% indicated that when making major decisions, they were either somewhat or very influenced by values associated with their religion.

Physicians represented general internists (32%), family practitioners (30%), neurologists (18%), psychiatrists (11%), geriatricians (5%), and other specialties (4%). Seventy-eight percent of the physicians saw their patients in a solo or private group practice; only 3% reported an HMO as their primary practice setting. Sixty-six percent of the doctors reported a practice size of 1,000 or more patients, with an overall median of 2,000. Within their practices, physicians recommended a number of substances for the possible prevention of memory loss, including Aricept (74.3%), estrogen (60.2%), vitamin E (59.6%), ginkgo (34.5%), Cognex (27.5%), nonsteroidal anti-inflammatory medications (24.6%), and vitamin C (18.7%).

All physicians in the study cared for patients with AD, with 51.6% reporting more than 25 AD patients currently under care. In addition, the responding physicians saw over three quarters of those patients with AD at least twice a year. Physicians were presented with a list of possible causes of AD and were asked to rate their level of agreement on a 4-point scale with the two upper values indicating agreement. Inheriting specific genes was the most highly endorsed causal factor followed by aging and then chance, strokes, and hardening of the arteries (Table 1).

Estimation of risk

Doctors were asked to estimate the chance of an asymptomatic 65-year-old developing AD over their lifetime, in two cases, one for whom there was no history of an affected parent

Table 1
Physician endorsement of possible causal factors for the development of AD

Possible causal factor	% Agree	% Disagree
Exposure to aluminum	9.7	90.3
Chance	45.8	54.2
Inheriting specific genes	95.3	4.7
Poisons in air/water supply	8.4	91.6
God's will	15.1	84.9
Aging	72.2	27.8
Poor diet	12.0	88.0
Not being mentally active	40.1	59.9
Hardening of arteries	42.5	57.5
Strokes	45.5	54.5
Hormone levels	28.9	71.1
Drinking too much alcohol	30.1	69.9
Injuries to the head	38.9	61.1

and the other for whom there was one affected parent. Table 2 presents the grouped risk estimates, using the same categories as Seshadri and colleagues for comparison. As can be seen, less than half of the physicians placed the risk estimate for those without an affected parent correctly, that is, between 11% and 20% (although the question is framed to reflect risk after the age 65, use of lifetime risk estimates as a standard is appropriate because virtually all the cases occur after the age of 65). Of those who were incorrect, the majority underestimated the risk. In the case for which there was a parent affected with AD, again slightly less than half of the physicians placed their estimate in the correct range. Other responses were evenly divided between overestimation and underestimation. Cross-tabulating these estimates, however, revealed only 35% of physicians providing estimates in the correct ranges for both conditions. A comparison of physicians with correct risk estimates and those with incorrect risk estimates failed to uncover any differences with respect to age, years since residency, specialty, familiarity with *APOE* or *PS1,* the number of AD patients treated, or the presence in their own family of a relative affected with AD.

Table 2
Estimates of lifetime risk for developing AD among 65-year-olds by status of parent

Risk estimate	Without affected parent	With affected parent
0%–10%	35.3	3.5
11%–20%	48.2[a]	20.0
21%–40%	8.8	48.2[a]
>40%	7.6	28.2

Values represent proportion of sample.
[a]Correct answer.

Use of currently available genetic tests

Physicians were informed that clinical laboratory testing was currently available for two genes associated with AD (*APOE* and *PS1*) and were queried specifically about their familiarity with these tests. Sixty-five percent of the respondents ($N = 110$) had heard of *APOE,* 33% had received literature about the test, and 18% had ordered at least one *APOE* test for a patient. In addition, 15.5% of physicians reported that an asymptomatic patient had requested *APOE* testing, and 5.3% had ordered at least one *APOE* test for an asymptomatic individual. Physicians who had heard about *APOE* ($N = 110$) estimated the risk for a person with a positive *APOE* test (PPV) to range from 8% to 95%, with a mean of 47.3% (SD = 20.4%).

A smaller subset of 61 physicians (37%) had also heard of *PS1,* 13% had received literature about the test, and 5% had ordered the test for a patient under evaluation. In addition, 4% had an asymptomatic patient ask for the test and 3% had ordered the *PS1* test for an asymptomatic relative of a patient with AD. For those physicians who indicated they had heard of *PS1* ($N = 61$), their estimated risk (PPV) that a person with a positive *PS1* test would develop AD ranged from 20% to 100%, with a mean of 53.5% (SD = 23.6%).

To examine physicians' understanding of the appropriateness of their use, respondents were asked to indicate how likely they would be to offer the *APOE* and *PS1* tests to individuals of varying clinical histories. The responses are presented in Table 3. Among the 110 physicians who had heard of the *APOE* test, over 90% indicated they would be unlikely to use the test for presymptomatic testing (Question 1). However, when it came to use of the test for diagnostic purposes (Questions 2 and 3), physicians seemed less sure of its correct use. A multiple logistic regression model was used to identify predictors of correct use for the situation described in Question 3, where use of the *APOE* test would be considered inappropriate; therefore, affirmative responses to this question are considered incorrect. Variables entered into the model included: estimate of positive predictive value for *APOE* test, knowledge of AD risk, number of AD patients treated yearly, propensity to recommend medications and other treatments for memory loss, medical specialty, recency of training, importance of religious values on decision-making, and belief in chance as a probable cause of AD. Only specialty proved to be significantly related to a correct response, with 53% of the neurologists and psychiatrists providing correct responses compared with 32% among other physicians ($\chi^2 = 4.22$; $P < 0.05$).

A second set of three questions pertained to *PS1* testing and responses for the 61 physicians who indicated they had heard of this test were analyzed. Among the smaller subset of physicians who indicated they had heard of the *PS1* test, the most likely case for its use was to assist with diagnosis of a young symptomatic patient. These physicians were only half as likely to offer this test for presymptomatic testing. Question 3 presents a case for which use of the *PS1* test is not appropriate; therefore, affirmative responses to this question are considered

Table 3
Physicians' stated propensity to order APOE and PS1 testing

	Likely (%)	Unlikely (%)	Appropriate
When considering the APOE test how likely would you be to:			
1. Offer the APOE test to an *asymptomatic* individual over the age of 65, with no family history of AD?	9.4	90.6	No
2. Offer the APOE test to a *symptomatic* individual over the age of 65 currently being evaluated for memory problems?	47.2	52.8	Yes
3. Offer the APOE test to a *symptomatic* individual under the age of 50 from a family with many cases of early AD?	58.5	41.5	No
When considering the Presenilin 1 test how likely would you be to:			
1. Offer the PS1 test to an *asymptomatic* individual under the age of 50 in a family with many cases of early AD?	39.3	60.7	Yes
2. Offer the PS1 test to a *symptomatic* individual under the age of 50 from a family with many cases of early AD?	66.0	34.0	Yes
3. Offer the PS1 test to a *symptomatic* individual between the ages of 50 and 65 with no family history of early onset AD?	32.1	67.9	No

Tabulation is limited to respondents who had heard of the specific test.

incorrect. Examination of predictors for responses to this question included: estimate of positive predictive value for *PS1* test, knowledge of AD risk, propensity to recommend medications and other treatments for memory loss, medical specialty, recency of training, importance of religious values on decision-making, and belief in chance as a probable cause of AD. As in the previous situation, the only significant predictor of a correct response was specialty training in psychiatry/neurology ($\chi^2 = 6.88$; $P < 0.01$); 83% of psychiatrists and neurologists answered correctly compared with 46% of other physicians.

Propensity to offer genetic tests with varying error rates

The physicians were asked to indicate the minimum level of PPV they believed should be achieved by a genetic test for Alzheimer's disease in order for that test to be offered in clinical practice. Responses ranged from 20% to 100%, with the median response 80%. Stepwise multiple regression was used to investigate the association of a number of characteristics with PPV. Physician responses were not correlated with recency of training, medical specialty, propensity to recommend medications and other treatments for memory loss, knowledge of AD risk, familiarity with *PS1* or *APOE* tests, belief in chance as a probable cause of AD or importance of religious values in decision-making. There was, however, a significant association between physician interest in higher PPV for a genetic test for AD and the evaluation and treatment of more than 25 AD patients yearly by the physician (68.7 vs. 79.1; $F = 12.94$, $P < 0.001$).

Subsequently physicians were asked about a range of predictive values applicable in their own practice with the use of vignettes. Physicians were told it was likely that, in the future, genetic tests would be developed for the purpose of identifying inherited factors that increase the risk of AD. Such tests involve uncertainty, and there may be false negatives (where the test fails to detect some people who will eventually develop AD), producing a test with <100% sensitivity, or the ability to detect all cases. There may also be false positives (where the test incorrectly classifies as a case individuals who will remain disease free) producing a test with <100% positive predictive value. Physicians were asked to assume that the test would be painless, inexpensive, and totally confidential. The vignettes were based on testing a group of 100 individuals, 13 of who would eventually develop AD and 87 of whom would not. In each case, physicians were asked if they would offer the test to their patients. The physician responses are shown in Table 4.

As can be seen from inspection of this table, approximately 84% of physicians would offer an error-free genetic test for AD to their patients. This percentage declined with increasing error rates, with the provision of false-positive results inhibiting propensity to offer the test more significantly than the provision of false-negative results.

We performed several multivariate logistic regression models with willingness to offer (1) a perfect test and (2) a test with 87% PPV (Question 5) as dichotomous outcomes. The test with 87% PPV, endorsed by 45% of respondents, was chosen because the proportion of respondents willing to offer the next best PPV (65%) dropped steeply to <15%. Predictor variables explored included time since residency, specialty board certification in psychiatry/neurology, familiarity with *APOE* and *PS1* testing, propensity to recommend medications and other treatments for memory loss, number of AD patients treated yearly, estimation of lifetime risk for AD, belief in chance as a probable cause of AD, and importance of religious values in decision-making.

Willingness to offer a test with 100% positive predictive value (PPV) and no false negatives (a perfect test) proved to be related to a physician's propensity to recommend substances for possible prevention of memory loss and increased impor-

Table 4
Physicians' willingness to offer genetic tests of varying error rates to their patients

Vignette	Offer test to your patients? Yes	No
Vignette 1		
1. Suppose a perfect test becomes available. That is, in the group of 100 individuals being tested, the 13 people who test positive go on to develop AD and the 87 people who test negative never develop AD. (PPV = 100%; Sensitivity = 100%)	83.5	16.5
In Vignettes 2–4, the test always assigns a negative result to the 87 people who will not develop AD, but a percentage of individuals who will develop AD go undetected. (PPV = 100%; Sensitivity 91%–31%)		
2. Test correctly identifies 12/13 who will develop AD	81.0	19.0
3. Test correctly identifies 9/13 who will develop AD	61.9	38.1
4. Test correctly identifies 4/13 who will develop AD	17.3	82.7
In Vignettes 5–7, the test always assigns a positive result to all 13 individuals who will develop AD; however, a percentage of the individuals who will not develop AD are misclassified. (PPV 87%–33%; Sensitivity = 100%)		
5. Test gives incorrect positive results to 2/87 who will not develop AD	46.1	53.9
6. Test gives incorrect positive results to 7/87 who will not develop AD	12.6	87.4
7. Test gives incorrect positive result to 26/87 who will not develop AD	7.8	92.2

tance of religious values in decision-making. Those recommending more antidementia treatments had a higher probability of offering a perfect test (91% vs. 78%; $\chi^2 = 4.80$; $P < 0.03$). There was a steadily increasing trend for willingness to offer the perfect test as role of religious values in decision-making increased (low, 75%; medium, 83%; high, 93%; χ^2 for trend = 6.23; df = 1; $P = 0.013$).

For offering the test with 87% PPV, familiarity with *APOE* testing was the only significant predictor, with an inverse relationship between familiarity and offering this test. The 53% of physicians with less familiarity with *APOE* testing would offer their patients a genetic test for AD with an 87% PPV, whereas only 36% of those physicians with greater exposure to *APOE* testing would offer such a test ($\chi^2 = 4.41$; $P < 0.04$). Notably there was no significant relationship between a physician's willingness to offer the 87% PPV test and the minimum level of positive predictive value they had earlier indicated should be achieved for a genetic test for AD for that test to be offered in practice. As reported above, the median positive predictive value for an acceptable test was 80%. This median acceptable PPV was nearly identical for those who would and would not offer the 87% PPV test.

DISCUSSION

As genetic susceptibility testing moves into clinical practice, physicians' understanding of susceptibility tests and the attendant recommendation and use of them becomes extremely important. Our findings indicate that a clear majority (65%) of physician respondents were familiar with *APOE* testing and unlikely to offer this test for asymptomatic individuals, in line with the current scientific and clinical recommendations.[24,27,34] Although fewer physicians were knowledgeable about the *PS1* test, the majority were also unlikely to use this test for presymptomatic testing. Even in cases where use of these tests would be indicated, no more than two thirds of physicians would likely order them; this finding suggests caution rather than overenthusiasm.

The survey does highlight several areas of concern, however. Physicians were asked to assess the conditional risk for an unaffected person aged 65 to become affected with Alzheimer's disease at some future time. Actuarially this is equivalent to requesting an estimate of the conditional lifetime risk, which adjusts for the failure to become affected before 65. Because the vast majority of AD cases do not manifest under the age of 65, the correct answer is approximately the same as the unconditional lifetime risk. Although most physicians are probably unfamiliar with the technical refinements of actuarial estimation, it is reasonable to expect them to know the approximate probability to become affected for a condition with such high frequency in the elderly. However, as in the earlier report by Seshadri et al.,[1] less than half of the physicians surveyed knew either the lifetime risk of AD or the change in risk when there is an affected parent; they generally underestimated the true risk. In addition, the endorsement of hardening of the arteries, strokes, and alcoholism as probable causes of AD by a third of physicians, suggests some difficulty discriminating AD from other types of dementia. Lack of knowledge regarding disease risk and etiology will likely impact physician recommendations for genetic testing.

Furthermore, physician estimates of risk, given a positive *APOE* or *PS1* test, were very similar, despite the contrasting implications of a positive finding in these two situations. Finally, there was the nontrivial rate at which physicians used *APOE* testing in asymptomatic individuals, possibly in response to patient demand. Almost one sixth of respondents had been asked to order this test under circumstances in which

testing is not recommended, and of these, nearly one third had indeed done this.

Concerns have been expressed that lack of knowledge, interest, or time on the part of physicians could compromise the introduction of AD genetic testing into clinical practice. In one of their first studies, a survey of 1,795 physicians in 10 states, Hofman and colleagues found that many nongeneticists showed decreased awareness and knowledge of genetics and genetic tests when compared with a standard based on genetically trained clinical personnel.[28] Our results indicate that among physicians who care for patients with AD, the majority are familiar with *APOE* testing and appropriately cautious about using this test. However, many fewer physicians are aware of *PS1* testing, and some respondents underestimated its definitiveness. The possible overuse of *APOE* testing, e.g., in asymptomatic persons, could result more from patient demand than from lack of knowledge by providers, although both factors may contribute to the problem.

The physicians surveyed, primarily middle-aged males in private practice, had substantial experience with the evaluation and treatment of AD patients in practice settings where risk to offspring and younger sibs would clearly emerge in many families. Although over 80% of these physicians would offer a perfect genetic test for AD, e.g., to confirm a clinical diagnosis or for a relative eager to know the future, there was little interest in genetic susceptibility testing when error rates climbed above the 20% margin. In fact, once hypothetical genetic tests for AD introduced error, physicians familiar with current genetic testing were more hesitant than their less-familiar colleagues to offer such a test. Physicians appear sensitive to the import of AD test results for their patients, being much less willing to offer tests that produce false-positive results. The majority of physicians were unwilling to offer a test with even a 2% false-positive rate, likely reflecting the absence of effective treatment for this condition.

Our findings revealed internal inconsistency regarding physicians' criteria for an acceptable error rate, perhaps raising a note of caution in the interpretation of these results. Physicians indicated that genetic tests for AD should have a minimum positive predictive value of 80% to be offered in clinical practice. However, this threshold was unrelated to physician interest in offering their patients a test with an 87% positive predictive value, a test which exceeds that threshold. The failure to find the expected association between these two suggests either that the pattern of responses reflects a distinction between a hypothetical or abstract opinion and contemplation of a professional course of action, or that the particular framing of the questions played a role in physician response.

Finally, it should be noted that even with the use of monetary incentives and repeated follow-up, less than half the physicians responded, perhaps limiting these findings, although it is not clear that increased response rates would necessarily alter our study findings.[32] Although it is only a speculative point, a response bias favoring physicians with greater interest in or knowledge of genetic testing would suggest that these findings may overestimate the current level of knowledge regarding genetics and AD among practicing physicians.

In summary, our results contain grounds for both optimism and pessimism regarding the future utilization of AD genetic susceptibility testing in clinical practice. Physicians do not appear to endorse widespread genetic testing under inappropriate conditions. Error rates larger than 20% were a strong discouraging factor, indicating the importance of accuracy to the clinician for such a grave prognosis. However, knowledge of disease risk and causal factors related to AD, as well as familiarity with well-known genetic etiologies, were less than satisfactory. Because at any one time there will be wide variation in knowledge of and readiness to offer these tests, our findings highlight the importance of creating new mechanisms for rapid diffusion of genetic testing information relevant to clinical practice.

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