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Genetic Testing for Alzheimer's Disease and its Impact on Insurance Purchasing Behavior

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Abstract

New genetic tests for adult-onset diseases raise concerns about possible adverse selection in insurance markets. To test for this behavior, 148 cognitively normal individuals participating in a randomized clinical trial of genetic testing for Alzheimer's disease (AD) were tracked for one year after risk

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assessment and APOE genotype disclosure. Although no significant differences were found in health, life, or disability insurance purchases, those who tested positive were 5.76 times more likely to have altered their long-term care insurance than individuals who did not receive APOE genotype disclosure. If genetic testing for AD risk assessment becomes common, it could trigger adverse selection in the long-term care insurance market.

INTRODUCTION

Progress in understanding the human genome and the recent development of genetic tests for susceptibility to adult-onset diseases have sparked debate in the public policy community regarding who should have access to genetic test results. Insurers argue that if they do not have access to such information, individuals who learn that they have tested positive for genes associated with an increased risk for serious adult-onset diseases would purchase greater amounts of insurance coverage at prices that are below an actuarially fair rate. That is, genetic testing has the potential to create adverse selection in an insurance market.

The Actuarial Standards Board defines adverse selection to be "the actions of individuals, acting for themselves or for others, who are motivated directly or indirectly to take financial advantage of the risk classification system."[1] For example, if people know they are at higher risk of dying from cancer at an early age then they might be more inclined to purchase life insurance to preserve wealth for surviving family members. If insurers are unaware of who might be engaging in this behavior, they would be unable to adjust their actuarial calculations and could face economic losses.[2]

Consumers and proponents of anti-genetic discrimination legislation argue that if genetic test results are shared with insurers, many consumers could be denied coverage or charged excessively high premiums for coverage. They note that distinctions made on the basis of genetic information are unfair because one's genetic makeup is immutable.[3] In addition, researchers worry that the fear of discrimination may lead individuals to decline to participate in important genetic studies.[4]

Concern about genetic tests and insurance issues has moved policymakers to take action. At the federal level, the 1996 Health Insurance Portability and Accountability Act (HIPAA) states that, for the group health plans covered by the legislation, genetic information cannot be considered a preexisting condition in the absence of a diagnosis of the condition related to the genetic information.[5] More recently, in October 2003, the U.S. Senate passed S. 1053, the Genetic Information Nondiscrimination Act with unanimous support and the House of Representatives is currently considering their version, H.R. 1910.[6] Despite bipartisan support, immediate prospects for these bills to become law appear dim.[7] Thirty-eight states have passed some form of legislation prohibiting the use of genetic information for risk selection and risk classification but only seven prohibit genetic discrimination in life insurance without actuarial justification; only three extend their protections to disability and long-term care insurance.[8] In sum, current public policy in this area is piecemeal at best.

Few empirical studies explore the validity of consumers' and/or insurers' claims. Studies of insurance discrimination have found mixed evidence on the question of insurance denial.[9] Two studies that explore the question of how women's life insurance purchasing behavior changed after learning that they tested positive for the BRCA1 gene mutation have also yielded mixed results.[10]

Before developing further policy regarding who should have access to genetic test results, it is vital that we gain a better understanding of the extent to which genetic testing precipitates adverse selection and/or discrimination in insurance markets. This paper examines the potential

for adverse selection in insurance markets in the context of testing for genetic susceptibility for Alzheimer's disease (AD).

Alzheimer's Disease

AD is a common late-onset, dementing disorder characterized by a progressive decline in cognition and functional abilities over 8–20 years.[11] Currently, at least 4.5 million individuals in the U.S. have AD and the direct medical costs of caring for AD patients are estimated to be as much as $100 billion per year. Costs are expected to rise in the future as it is estimated that 13.2 million people will have the disease by 2050.[12]

The three most important risk factors for AD are increasing age, a family history of AD, and the presence of a specific allele of the Apolipoprotein E (APOE) gene. Every individual has one maternally and one paternally inherited APOE allele of type ε2, ε3, or ε4. The ε4 allele confers increased susceptibility to development of AD, but is neither necessary nor sufficient to cause AD. The presence of one ε4 allele increases the risk of developing AD two-to-threefold, while having two ε4 alleles increases the risk to 15-fold or higher in Caucasian populations. The ε4 allele is found in approximately 15% of the population and over half of clinically diagnosed Alzheimer's patients. [13]

DATA AND METHODS

Study Design

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study is a recently completed randomized trial evaluating the impact of a genetic education and counseling program for adult children of AD patients.[14] It is the largest study of its kind to date. As such, it provides a rare opportunity to gain initial insights into the relationship between genetic testing for AD and insurance purchasing behavior.

Participants in the REVEAL Study were either self-referred or systematically ascertained through their family's membership in existing AD research registries in Boston, Cleveland, or New York City. Recruitment began in August 2000 and the last of the follow-up respondent surveys was completed in October 2003. A total of 162 participants were randomized into the clinical trial.[15] All participants in the study were at higher than average risk for developing AD because the protocol required all participants to have at least one parent affected by AD.

In the control arm of the REVEAL study, participants were informed of their risk of developing AD based on gender and family history alone, with lifetime risk estimates ranging between 18% and 29%. Meanwhile, intervention group participants learned their APOE genotype and were informed of their risk on the basis of gender, family history, and genotype, with lifetime risk estimates ranging from 13% to 57%.[16]

Of the 162 individuals in the study, 148 were included in the analyses that follow. The remaining 14 were excluded because they had missing data on one or more of the covariates. Among the 148 individuals, 46 were in the arm of the study where there was no APOE disclosure, 54 learned that they were ε4 negative, and the remaining 48 learned that they were ε4 positive (i.e., had one or two ε4 alleles).[17]

Participants' socio-demographic information presented in Exhibit 1 illustrates that the REVEAL sample, like all research volunteer samples, is *not* a random sample of the population. Individuals in this study were more likely to be white, female, and well-educated than members of the general population. Participants were also typically older that the general population, since participants had to be an adult child of a diagnosed AD patient. Before intervention it was ascertained that 97% of the sample had health insurance, 78% had life insurance, 40% had

disability insurance, and 19.8% had long-term care insurance.[18] These high rates of insurance coverage likely reflect the atypical age, education, and ethnic composition of the sample.

The REVEAL Study was approved by the Institutional Review Boards for human research protection at each participating institution. It was also monitored by an Ethics Advisory Board. Participants gave informed consent and were assured the protection of their genetic information through standard research confidentiality protocols as well as by an NIH Certificate of Confidentiality.[19] Genetic counselors presented semi-scripted education sessions that described APOE testing and the REVEAL Study research protocol. The possibility of genetic discrimination was mentioned by the counselors and in the study consent form, but in neither case was it described in detail. Education sessions also focused on the possible benefits, risks, and limitations of genetic susceptibility testing, including the current lack of preventive options for AD. All counseling was non-directive. Counseling did not explicitly focus on insurance issues.

Primary outcome measures in the REVEAL Study focused on determining the social and psychological impact of learning one's genotype. Additional study measures evaluated changes participants reported making, or planned to make, in health, life, disability, and long-term care insurance following risk disclosure. These questions were asked in interviews that occurred six weeks, six months, and one year after risk disclosure. We used responses from all three questionnaires to construct variables that measured whether or not a respondent ever changed or ever thought about changing insurance coverage during the first year following risk assessment and disclosure.[20]

Given that study participants knew their test results but insurance companies did not, proponents of the adverse selection theory would predict that participants who tested positive for the ε4 allele would be more likely to increase their insurance coverage than those who tested negative or participants who did not receive APOE disclosure. We tested this hypothesis using a multivariate logit model that examined the impact of testing status on insurance changes controlling for possible confounding factors (e.g., marital status, age, sex, education).[21]

STUDY RESULTS

Exhibit 2 shows the bivariate results. In the case of health insurance, life insurance, and disability insurance, we found no significant differences in reported insurance changes by disclosure status. When the respondents were asked if they were "thinking about" making changes, no significant differences were found between the groups in the health and disability insurance categories. Those who tested positive for the ε4 allele, however, were moderately more likely to be thinking about changing their life insurance coverage ($p<.10$). Long-term care insurance was the one domain where individuals who tested positive for the ε4 allele reported having made more changes ($p<.05$), and to have been thinking about making changes ($p<.05$).

Multivariate Analysis

Exhibit 3 shows the estimated odds ratios for the long-term care insurance logits. These estimates control for testing status and covariates that may also be associated with long-term care insurance changes. Exhibit 3 reveals that participants who learned they had tested positive for the ε4 allele were more likely than individuals who did not receive disclosure information to have reported making changes in long-term care insurance ($p = .0511$) even after controlling for marital status, age, sex, education, concern about developing AD, past/present experience as an AD caregiver, and whether or not the respondent had any long-term care insurance at baseline. In contrast, the bivariate relationship between APOE disclosure and thinking about changing long-term care insurance disappeared when we controlled for these covariates.

Given the modest sample size, sensitivity tests were run to determine if the estimated relationship between testing positive for the ε4 allele and making changes in long-term care insurance was robust. Bootstrap estimates of the long-term care insurance change equation presented in Exhibit 3 reveal that our results are only suggestive.[22] Definitive confirmation of our result must await larger, more socio-demographically diverse samples.

DISCUSSION AND POLICY IMPLICATIONS

This is one of only three empirical investigations of the extent to which genetic testing for adult-onset diseases contributes to adverse selection in insurance markets. Of these, it is the only study to employ a randomized clinical trial methodology. As such it adds to the small, but growing literature on genetic testing and adverse selection and offers the following policy implications.

First, there was little evidence of adverse selection in the health, life, and disability insurance markets despite the fact that the sample consisted of highly motivated individuals (i.e., all had a family history of AD and were highly educated) who were participating in a closed research trial where confidentiality of genetic information was guaranteed. This finding might be expected, however, given the age of participants, the relatively short period of follow-up (i.e., one year), individuals' typical insurance buying patterns, and the unique attributes of various insurance products.[23]

Second, the one insurance domain where we find suggestive evidence of adverse selection is long-term care. Almost 17 percent of those who tested positive subsequently changed their long-term care insurance coverage in the year after APOE disclosure, compared to approximately 2 percent of those who tested negative[24] and 4 percent of those who did not receive APOE disclosure. The overall percentage with long-term care insurance rose from 19.8% at baseline to 27% just one year later.[25] Roughly three-quarters of this increase is attributable to study participants who learned they had tested positive for the ε4 allele. Controlling for other insurance related covariates, we found that individuals who tested positive were 5.76 times more likely to change their long-term care insurance coverage during the subsequent year than were individuals who did not receive APOE disclosure (although this finding is not reinforced by the sensitivity analyses).

Policymakers who are attempting to balance consumers' concerns regarding potential genetic discrimination against insurers' concerns that the withholding of genetic test results would make insurance markets unprofitable should proceed with caution. Our findings imply that the potential for adverse selection may vary considerably by insurance market thus making it difficult to design a public policy that works well in all instances.[26]

It may be that the natural history of AD combines with APOE testing and the characteristics of the mostly private long-term care insurance market to create the "perfect storm" with regard to adverse selection. That is: (1) AD is a condition that has a high probability of requiring formal, long-term care services, (2) APOE testing gives significant, albeit incomplete, predictive information for the at-risk population, and (3) long-term care insurance is generally a private insurance market where an information asymmetry can have serious consequences. Taken in combination, these conditions create a situation where adverse selection may occur and where its consequences for insurers and consumers may be significant. This premise is consistent with the fact that we observe a positive relationship between testing positive and changing one's long-term care insurance coverage even in our relatively small sample.

Currently, APOE genotyping for risk assessment is not recommended in asymptomatic individuals, but the field of AD research is moving toward risk profiling and preventative

treatments, so this could change.[27] With 15% of the population carrying the ε4 allele, would widespread APOE testing affect the viability of the long-term care market? Long-term care insurance pricing for AD depends on factors such as population incidence, claims experience, and estimates of the degree of adverse selection. A definitive estimate of the degree of potential adverse selection in this market cannot be ascertained until more empirical work is done with samples that include socioeconomically and demographically diverse segments of the population. But, we do know that AD is responsible for the longest, most common, and most expensive long-term care insurance claims.[28] Significant increases in higher risk policyholders would be accompanied by increases in long-term care insurance costs. How these increased costs would be shared among policyholders at higher or lower risk of AD, and whether prices would reach a level that is unattractive to most buyers, would depend on business and public policy decisions that are beyond the scope of this study.

If genetic testing for AD becomes more commonplace, it would likely precipitate the call for further policy action in the area of genetic testing and insurance. Those making policy choices would be faced with the dilemma of whether to handle genetic risk in insurance through market stratification driven by an absence of policy rules or by imposing rules (e.g., nondiscrimination laws, mandatory universal coverage, mandatory disclosure of genetic test results to insurance companies in the case of large policies). In making these choices, policymakers would need to balance considerations regarding consumers' rights to protect themselves from uncontrollable health risks with the insurance industry's adverse selection concerns that could affect product affordability.

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8. For listing of state bills and a description of their scope see National Conference of State Legislators: State Genetic Non-Discrimination in Health Insurance Laws http://www.ncsl.org/programs/health/genetics/ndishlth.htm, accessed August 13, 2004. Typically these statutes focus on health insurance and potential employer discrimination. Only Massachusetts, Montana, and New Mexico extend their prohibitions to disability and long-term care insurance. Additionally, Colorado, Massachusetts, Oregon, and Vermont prohibit insurers from requiring applicants to undergo genetic testing for long-term care insurance but permit the use of test results. Finally, some states have specific exclusions for life, disability, or long-term care insurance in their genetic nondiscrimination legislation. National Conference of State Legislators: State Genetic Non-Discrimination Laws in Life, Disability and Long-Term Care Insurance http://www.ncsl.org/programs/health/genetics/ndislife.htm accessed August 13, 2004.
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17. Having two ε4 alleles raises the risk of developing AD more than having one ε4 allele. There were only three individuals in the ε4 positive group who had two ε4 alleles. Their small numbers precluded undertaking analyses comparing the insurance behaviors of those with two ε4 alleles to other study participants.
18. Nationally, only 7% of individuals age 65 and older carry long-term care insurance. M. Niefield, et. al., "Long-Term Care: Medicaid's Role and Challenges," Kaiser Commission on Medicaid and the Uninsured Report (November 1999).The fact that our respondents' initial holdings were almost three times the national average reinforces our contention that the REVEAL sample is not representative of the general population.
19. This certificate allows "the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding whether at the federal or state or local level." National Institutes of Health Office of Extramural research. http://grants1.nih.gov/grants/policy/coc/index.htm accessed on September 28, 2004.
20. Individuals were included in the analysis if they responded to any of the insurance change questions and if they did not have missing data on any of the covariates. If an individual's insurance responses

were missing at either the six-month interview or the one-year interview, his/her response from the preceding interview was used to measure insurance change.

21. A logit estimating routine is used because of the qualitative nature of the dependent variable (i.e., 1= yes, 0=no). See W.H. Greene, Econometric Analysis (New York, NY: Macmillan Publishing Company, 1993).
22. Using bootstrap estimation with 10,000 replications, we obtained an odds ratio estimate associated with testing positive for the ε4 allele of 1.75. The bias-corrected (BC) 95% confidence interval estimation for this estimate was −1.42 to 19.8. Since this interval includes zero, we must be cautious in our interpretation of the logit regression results.
23. Health insurance is typically obtained through an employer with no underwriting and disability insurance would typically play a very small role in providing coverage for a late-onset progressive disease like AD. The need for additional life insurance would also likely be minimal given that in most instances children would have been raised and the mortgage would have been paid off by the time this late onset disease strikes. In contrast, long-term care insurance is designed specifically to protect financial assets and to minimize care-giving burdens of close family members late in one's life. For all of these reasons, individuals in our sample who had the ε4 allele of the APOE gene are not likely to see any economic need to alter health, disability, or life insurance coverage.
24. A careful review of the open-ended responses to the insurance questions found no instances where participants who were ε4 negative decreased their insurance coverage during the year.
25. Since a genetic test result is permanent, it is quite possible that these percentages would increase over time. In particular, individuals who learned their genetic test results at a relatively young age (e.g., prior to age 50), may believe that they need not change their long-term care insurance holdings in the short term.
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Exhibit 1

Socio-Demographic Characteristics

Demographic Characteristics	No APOE Disclosure (N=46)	ε4 Negative (N=54)	ε4 Positive (N=48)	Total Sample (N=148)
Fraction Currently Married	.63	.63	.73	.66
Mean Respondent Age (measured in years) [a]	54	53	50	52
Fraction of Male Respondents [b]	.22	.40	.21	.28
Respondents' Mean Years of Schooling	17	17	17	17
Fraction Who are Past or Present AD Caregiver	.78	.80	.67	.75
Mean Baseline Worry About Developing AD (5=strongly agree, 1=strongly disagree) [c]	3.9	3.8	4.2	4.0

Source: REVEAL Study.

[a] An ANOVA test for age differences by testing status was statistically significant: F=2.29, p< .10.

[b] A Chi-square test for sex differences by testing status was statistically significant: $I^{I} = 6.4$, p<.05.

[c] An ANOVA test for baseline worry about developing AD differences by testing status was statistically significant: F=2.48, p<.10.

Exhibit 2

Fraction of Participants Who Thought about Changing Insurance Coverage or Actually Changed Insurance Coverage Over a One Year Period Stratified by Testing Status.

	Percentage Reporting an Actual Change APOE Genotype			Percentage Reporting S/he is AThinking About@ Making a Change APOE Genotype		
	No APOE Disclosure	ε4 Negative	ε4 Positive	No APOE Disclosure	ε4 Negative	ε4 Positive
Health Insurance	6.52	5.56	12.50	23.9	13.0	25.0
Life Insurance[a]	6.52	7.41	2.08	4.35	5.56	16.67
Disability Insurance	4.35	3.70	4.17	8.70	7.41	18.8
Long-Term Care Insurance[b]	4.35	1.85	16.7	32.6	22.2	45.8

Source: REVEAL Study.

[a] The Fisher's Exact Test for thinking about making changes in life insurance coverage by testing group was statistically significant at p< .10.

[b] The Fisher's Exact Tests for actual changes in long-term care insurance coverage and thinking about making changes in long-term care insurance coverage by testing group were both statistically significant at p<.05.

Exhibit 3

Odds Ratio Estimates from the Logit Regressions (95% confidence intervals in parentheses).

Independent Variables	Changed Long-Term Care Coverage (1=yes) (N=143)	Thinking About Changing Long-Term Care Coverage (1=yes) (N=123)
Currently Married (1=yes, 0=no)	0.64 (0.13 B 3.17)	1.34 (0.59 B 3.03)
Age (measured in years)	1.03 (0.95 B 1.12)	0.98 (0.93 B 1.02)
Sex (1=male; 0=female)	1.22 (0.20 B 7.58)	0.73 (0.30 B 1.82)
Education (measured in years)	1.08 (0.78 –1.50)	1.24** (1.04 B 1.48)
Has Long-Term Care Insurance At Baseline (1=yes, 0=no)	6.79** (1.45 B 31.24)	0.36* (0.12 B 1.09)
Past or Present AD Caregiver (1=yes, 0=no)	1.00 (0.21 B 4.70)	1.03 (0.42 B 2.51)
Baseline Worry Scale About Developing AD (5=strongly agree, 1=strongly disagree)	1.13 (0.54 B 2.38)	1.07 (0.73 B 1.57)
ε4 Negative[a] (1=yes; 0=no)	0.36 (0.028 B 4.58)	0.62 (0.24 B 1.60)
ε4 Positive[a] (1=yes, 0=no)	5.76* (0.99 B 33.50)	1.56 (0.63 B 3.90)
Equation χ^2	18.44**	19.48**

Source: REVEAL Study.

* $p < .10$

** $p < .05$

[a] The omitted group in this sequence of dummy variables are those individuals who did not receive APOE disclosure.