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Genetic Risk Assessment for Adult Children of People With Alzheimer's Disease: The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study

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ABSTRACT

As genetic risk factors continue to be identified for common, complex adult-onset diseases, it will become increasingly important to understand if, how, and when to translate these discoveries into clinical practice. This article provides an overview of and results to date from the REVEAL study, a multisite randomized clinical trial (n = 162) examining the impact of a genetic risk assessment program, including apolipoprotein E genotype disclosure, for adult children of people with Alzheimer's disease. The study's rationale and procedures are described, including the generation of numerical lifetime risk curves for use in the education and counseling protocol. Findings are summarized across numerous study questions, including (1) who seeks genetic risk assessment and why, (2) how apolipoprotein E results affect risk perceptions, (3) the psychological impact of genetic risk assessment, and (4) how risk information affects participants' subsequent health and insurance behaviors. (*J Geriatr Psychiatry Neurol* 2005; 18:250-255)

Keywords: Alzheimer's disease; genetic testing; apolipoprotein E; risk assessment

Genes and other biological markers are rapidly being identified that can provide presymptomatic estimates of risk to individuals for the eventual development of complex late-onset diseases.[1] There may be considerable public interest in obtaining risk information, particularly as treatments are developed to slow or prevent the onset of degenerative diseases.[2] Many of the recently discovered gene markers do not definitively predict future disease (eg, as in genetic testing for Huntington's disease), but they are associated with increased risk of various diseases (eg, breast and colon cancers). Testing for such genes therefore requires different protocols for providing risk assessment and counseling. With few restrictions on the marketing and use of such tests, their usage may soon

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increase. More information is needed to help us understand who would seek such genetic risk information once available, and why they would do so. In addition, it will become increasingly important to determine the benefits and negative consequences of providing genetic risk information in order to inform clinical guidelines and public policy in this arena.

Most work to date in this area has focused on genetic testing for cancer. However, it will be important to consider other disease contexts as well, where age of onset may be later, prevalence higher, and risk information less certain. Alzheimer's disease (AD) is a case in point. Recent advances in genetic research on AD have brought about the possibility of susceptibility testing for asymptomatic individuals.[3,4] The apolipoprotein E (APOE) ε4 allele on chromosome 19 is a risk factor for AD whose impact has been widely confirmed.[5,6] Although the presence of ε4 alleles significantly increases risk of AD compared with other APOE genotypes (most estimates range from twofold to eightfold), it is neither necessary nor sufficient to cause the disease.[7] The APOE ε4 allele is thus distinct from the very rare mutations that inevitably cause AD, typically with early onset.[8] Susceptibility testing for AD therefore differs in important ways from predictive testing for disease-causing genes; it is relevant to a much larger at-risk population yet provides much less certain risk information than predictive testing.[9] This limitation, coupled with a general lack of treatment options for AD, has prompted several consensus statements cautioning against the premature introduction of susceptibility testing in asymptomatic individuals.[10-12] However, given treatment advances, potential patient demand, and clinical trials seeking "enriched" at-risk samples, there is a need to examine genetic risk assessment for AD in a research context.[13]

STUDY OVERVIEW

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study is the first randomized controlled trial (RCT) to evaluate the impact of risk assessment for AD using APOE genotype disclosure for AD. The study protocol was developed by a team of experts in the fields of neurology, genetics, genetic counseling, psychology, and bioethics. Protocol development was overseen and approved by an External Advisory Board and institutional review boards at each original study site (Boston, New York, Cleveland).

Participants and Procedures

All study participants were adult children of a person with clinically diagnosed and/or autopsy-confirmed AD. Figure 1 shows how participants entered and progressed through the study. Participants entered the study in 1 of 2 ways: (1) self-referral after hearing about the study through the media, public presentations, or word of mouth; or (2) systematic contact through their family's membership in AD research participants attended a formal education session conducted by the site's genetic counselor (GC), where information about AD and the study protocol was provided using a standard slide show presentation. Here the GC stressed the distinction between susceptibility and more predictive types of testing for AD and discussed the possible benefits and limitations of susceptibility testing. Following the education session, interested participants progressed to the counseling/blood draw stage of the study, which involved individualized genetic counseling and blood draw for APOE genotyping. At this stage, participants were also screened for cognitive and psychiatric functioning, to ensure that risk information would not be disclosed to cognitively impaired or psychiatrically vulnerable populations.

A total of 162 participants (mean age = 53 years; 72% female; 94% white; mean education = 16.7 years) was randomized to either the intervention or control arm of the study. Participants randomized to the intervention arm received genetic counseling and risk assessment based on their gender, family history of AD, and APOE genotype, whereas those randomized to the control arm received genetic counseling and risk assessment based only on their gender and family history. In each arm, the GC met individually with participants in 30- to 60-minute risk disclosure sessions to communicate risk, provide support, and answer questions.

Development of Risk Estimates

Risk estimates were provided to participants in oral, written, and visual formats; educational materials included risk curves showing participants' risk of AD up to age 85 compared with other first-degree relatives and the general population.[14] To create these curves, we drew on previously published estimates of gender- and age-specific family risk.[7,15-18] We used 2 sources of information to develop the risk curves: (1) gender- and age-specific incidence curves for first-degree relatives of persons with AD (comparable to those previously published)[15,17-18] and (2) APOE genotype-specific odds ratio estimates for each gender and age reported in a meta-analysis of data from more than 50 studies worldwide.[7] Lifetime risk estimates provided to participants ranged from 13% to 57%. Additional details on the generation of study risk curves are provided elsewhere.[14] Figures 2-7 display sample risk curves as they were presented to participants (without confidence intervals, however, in order to simplify the visual message).

FINDINGS TO DATE

Reasons for Seeking Risk Assessment

Prior surveys have suggested numerous reasons first-degree relatives might choose genetic testing for AD,[19] but the REVEAL study offered the first chance to assess these

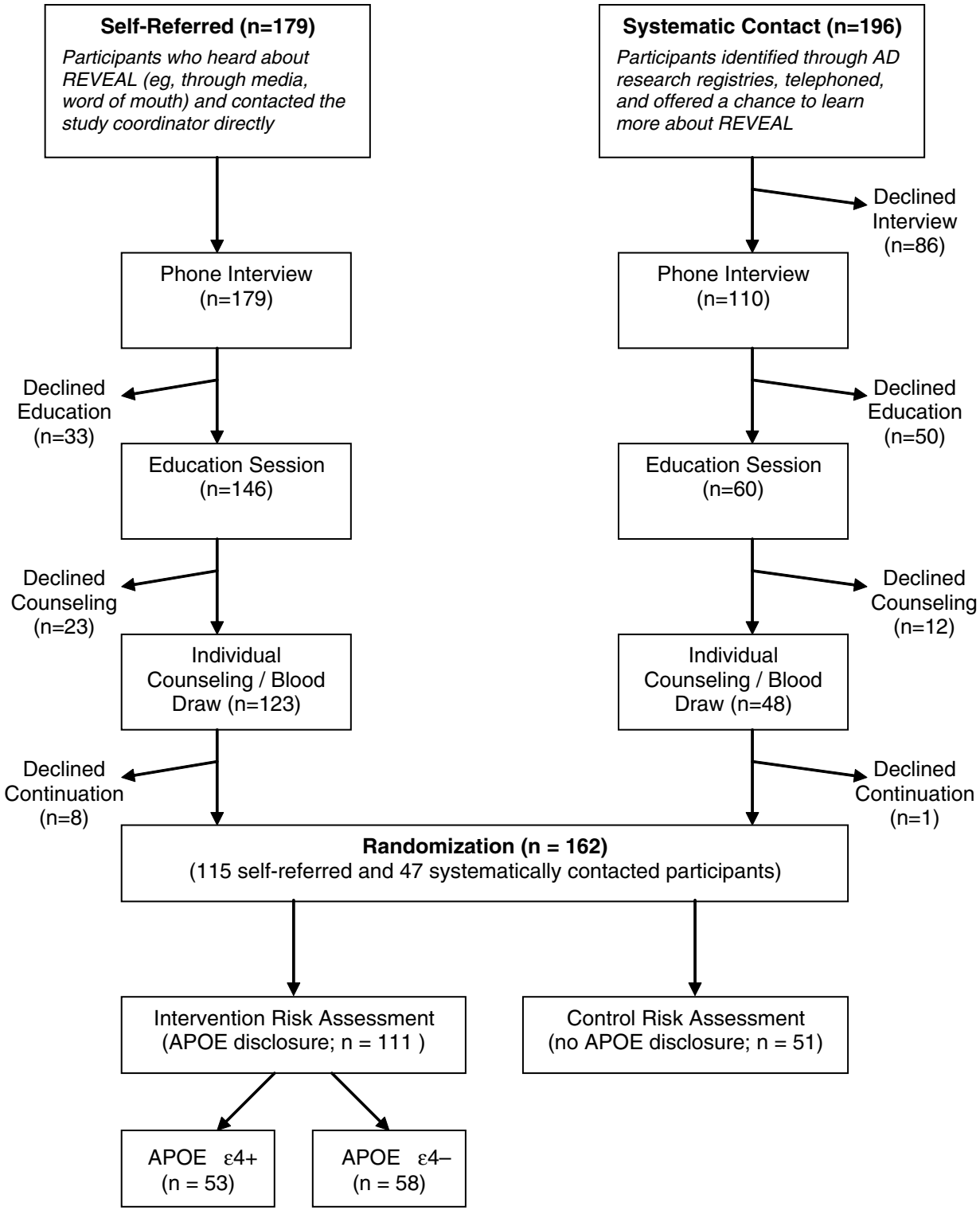

Figure 1. Participants' progression through the REVEAL study. AD, Alzheimer's disease; APOE, apolipoprotein E.

motivations among participants who were actually offered testing. At the education session before enrollment in the RCT, we asked participants to rate the importance of 12 possible reasons they might want to seek genetic risk assessment for AD. Reasons listed were derived from our previous survey research on the topic,[9,19] and commonly endorsed reasons in this study included (1) to arrange personal affairs (87.4%), (2) the hope that effective treatment will be developed (86.8%), (3) to arrange long-term care (81.4%), (4) to prepare my family for the possibility of my illness (77.8%), (5) to do things sooner than planned (75%), and (6) relief if I learned I was at lower risk (69.6%). Women strongly endorsed more reasons for seeking testing than men ($P < .05$). Findings suggest at-risk individuals

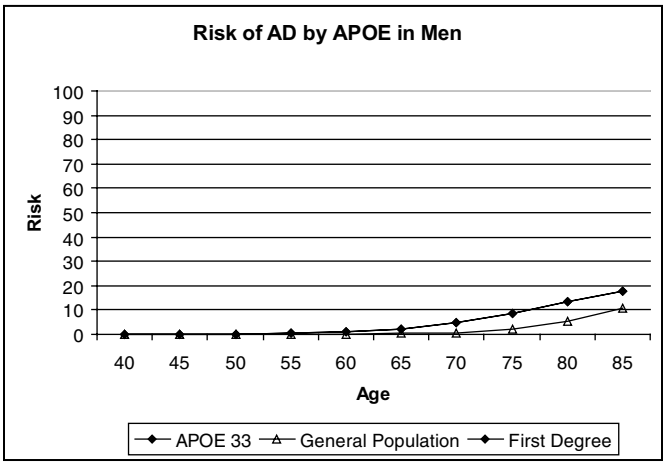

Figure 2. Risk curve for male, ε3/ε3 genotype. The ε3/ε3 genotype risk curves completely overlap with the first-degree relative curves; thus, only two distinct curves are depicted on these graphs. AD, Alzheimer's disease; APOE, apolipoprotein E.

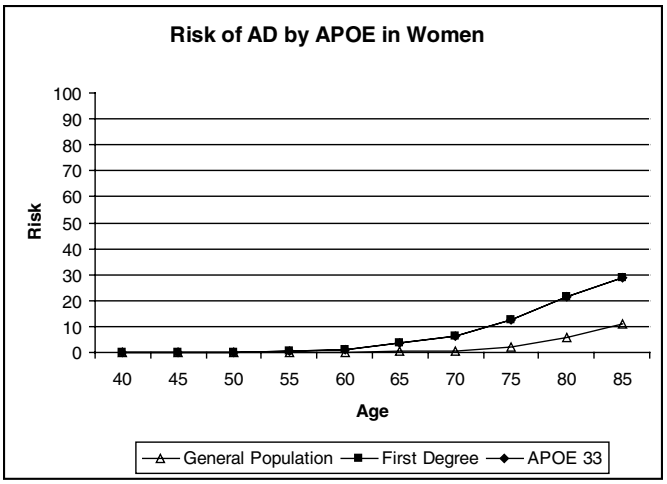

Figure 3. Risk curve for female, ε3/ε3 genotype. The ε3/ε3 genotype risk curves completely overlap with the first-degree relative curves; thus, only two distinct curves are depicted on these graphs. AD, Alzheimer's disease; APOE, apolipoprotein E.

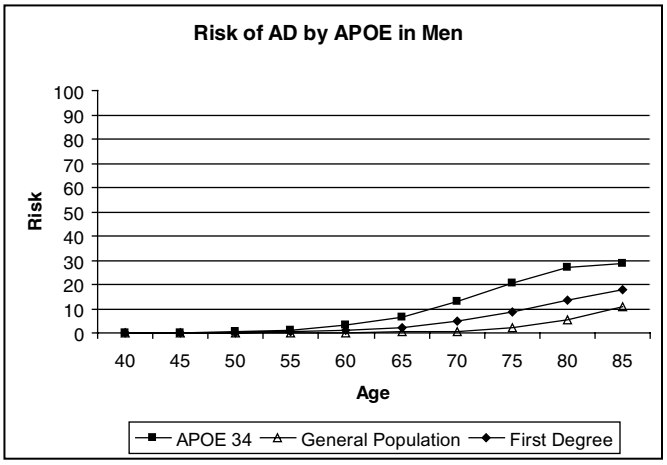

Figure 4. Risk curve for male, ε3/ε4 genotype. AD, Alzheimer's disease; APOE, apolipoprotein E.

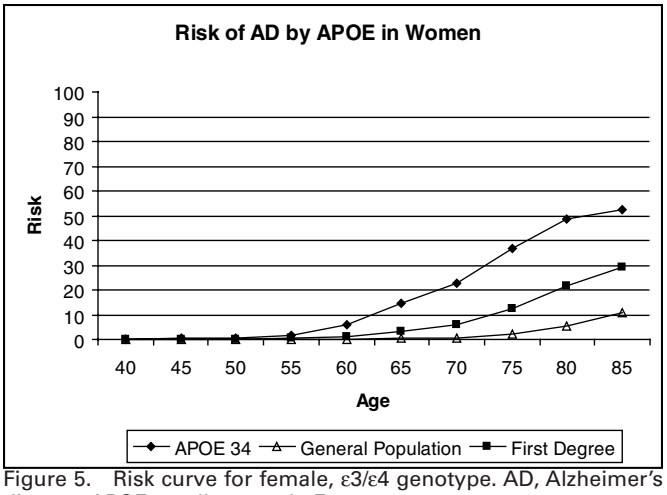

Figure 5. Risk curve for female, ε3/ε4 genotype. AD, Alzheimer's disease; APOE, apolipoprotein E.

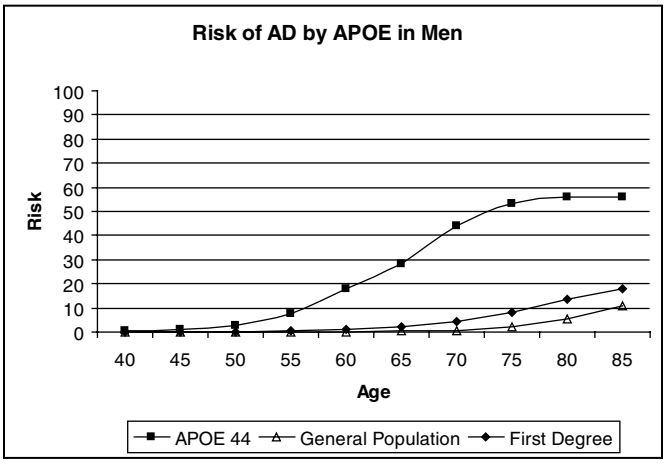

Figure 6. Risk curve for male, ε4/ε4 genotype. AD, Alzheimer's disease; APOE, apolipoprotein E.

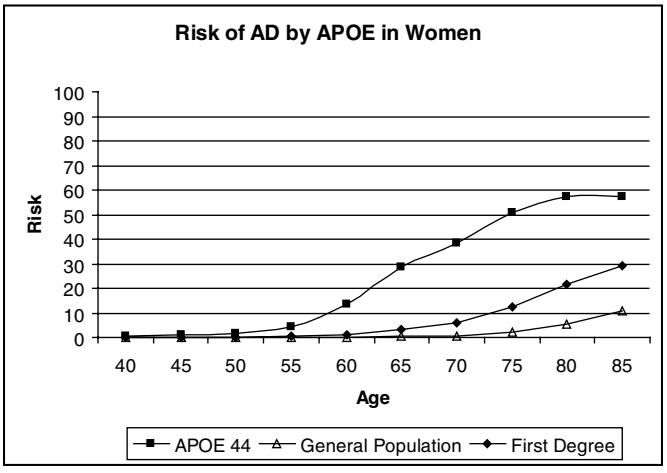

Figure 7. Risk curve for female, ε4/ε4 genotype. AD, Alzheimer's disease; APOE, apolipoprotein E.

are primarily interested in AD susceptibility testing for reasons not directly related to their medical care but for reasons related to advance planning and emotional coping with the threat of disease.[20]

Interest in Risk Assessment

We gauged interest in risk assessment by following 2 groups of participants from initial contact to enrollment in the RCT: those who were systematically contacted through research registries (n = 196), and those who were self-referred (n = 179). The 47 systematically contacted participants (24%) who progressed from initial contact to enrollment were more likely to be below age 60 (adjusted odds ratio = 3.83, $P < .01$) and college educated (adjusted odds ratio = 3.48, $P < .01$) than those who did not progress to enrollment. Of 179 self-referred participants, 115 (64%) progressed from initial contact to enrollment. Most self-referred participants had a college education and were female (79%). These findings suggest that susceptibility testing for AD may be of particular interest to women, college educated persons, and persons below age 60.[21]

Risk Perceptions

To gauge the impact of providing a "negative" test result for AD (ie, no ε4 allele), we conducted a subanalysis of 66 women, all of whom received a 29% lifetime AD risk estimate, but only some of whom received their APOE genotype (ie, 36 women with ε3/ε3 test results, whose APOE information did not alter their lifetime risk estimates). Compared with the women who did not receive APOE information, and despite having received an identical numerical lifetime risk estimate, the ε3/ε3 women perceived their risk as lower, reported testing as having a more positive impact, endorsed less strongly the belief that they might develop AD, and reported a greater reduction in anxiety about AD (all $P < .05$).[22] Related analyses suggested that receiving ε4-negative test results tended to lower participants' sense of their AD risk, but that ε4-positive results did not necessarily elevate participants' sense of risk (possibly because they already entered the study with high perceived risk).[23] Preliminary analyses regarding the comprehension and retention of risk information have also suggested that participants' recall of their APOE genotype was superior to their recall of lifetime risk estimates.[24] These findings highlight the powerful effects that genotype information can have on participants, even when delivered in a multivariable risk assessment.

Insurance Changes

We examined participants' reported insurance changes in the 12 months following risk disclosure. Few participants reported changes regarding health (8%), life (5%), or disability insurance (4%), with no group differences in these domains. The ε4-positive group, however, was more likely to report changes in long-term care (LTC) insurance than the ε4-negative group or controls (17% vs 2% vs 4%, $P < .05$). Should susceptibility testing for AD become available, these results suggest that policy makers will need to address issues of adverse selection by consumers and genetic discrimination by insurers in the LTC insurance market.[25]

Health Behaviors

We have conducted preliminary analyses of self-reported health behavior changes within a year after risk disclosure. These suggest that participants found to be at higher risk for AD were more likely to report engagement in subsequent activities believed to potentially reduce risk of AD (eg, adding vitamin E, changing diet or exercise). Fifty-three percent of participants who tested ε4 positive reported at least 1 behavior change for AD prevention, compared with 24% of ε4-negative participants and 31% of controls ($P < .05$). Findings suggest that AD risk information may motivate engagement in risk reduction activities.

Psychological Impact of Risk Assessment

Preliminary analyses suggest that risk assessment and genotype disclosure did not adversely affect the psychological well-being of participants.[26,27] We compared results among 3 study groups: control arm participants, intervention arm participants who tested positive for the ε4 allele, and intervention arm participants who tested negative for the ε4 allele. There were no significant posttest group differences in depression or anxiety symptoms, and all group means were well below clinical cutoff scores at all 3 time points (6 weeks, 6 months, and 1 year following risk disclosure). A few participants experienced significant increases in depression or anxiety symptoms following risk disclosure, but interviews with study GCs indicated that these changes were primarily attributable to external stressors (eg, death in the family, response to 9/11 tragedy).

Related analyses were conducted on the impact of risk disclosure on participants' anxiety about developing AD. On a commonly used measure of test-related distress, the ε4-negative group scored lower than the ε4-positive group or controls at all time points, with all group mean scores below clinical cutoffs. Following risk disclosure, nearly 90% of all participants reported the same or lower anxiety about developing AD compared with baseline, with the ε4-negative group particularly likely to report lower anxiety.[28] These findings suggest that most participants experienced the same or lower levels of anxiety about AD following risk disclosure.

FUTURE DIRECTIONS

A second REVEAL clinical trial is now underway, in which we are comparing our original protocol to a more clinically feasible "condensed" protocol. We have modified recruitment strategies so that our sample will include more

African Americans (Howard University is now a study site) and older adults than before. Customized risk curves for African Americans have been developed, and instruments more sensitive to the impact of genetic testing have been added to the study protocol.[29] In addition, risk disclosure sessions are now being audiotaped to allow for examinations of the process of genetic risk assessment using well-established coding methods such as the Roter Interaction Analysis System.[30] Finally, given the limited numbers of genetic counselors nationwide, we are exploring the impact of physician-provided genetic risk disclosure. Given physicians' limited time, we have developed more elaborate take-home educational materials to be provided to participants before risk disclosure, allowing physicians to routinely complete disclosure sessions in 10 to 20 minutes. Finally, we are attempting to recruit more systematically from hospital outpatient clinics (rather than research registry volunteers) to increase generalizability of study results.

As we learn more about genetic risk for human diseases, understanding how people respond to such information will be crucial to effectively translate genetic discoveries into clinical care. Research efforts such as the REVEAL study may provide guidance as we consider if, how, and when to incorporate genetic markers into clinical risk assessment programs.

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