

**Comparing Self-Referred and Systematically Recruited Participants in
Genetic Susceptibility Testing Research:
Implications for Uptake and Responses to Results**

by

Kurt Derek Christensen

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Doctoral Committee:

**Associate Professor Scott Roberts, Chair
Professor Sharon Reilly Kardia
Assistant Professor Brian J. Zikmund-Fisher
Colleen M. McBride, National Human Genome Research Institute**

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DEDICATION

This dissertation is dedicated to my mother, Anda.

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ABSTRACT

Studies examining whether genetic susceptibility testing for common, complex diseases can motivate individuals to improve health behaviors and advance planning have shown mixed results. An understudied area that may help reconcile these differential findings involves how testing was initiated. The overall goal of this dissertation was to understand the implications of different sampling strategies by examining self-referred versus systematically recruited populations in genetic susceptibility testing research. Using data from the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study, a series of randomized controlled trials exploring genetic susceptibility testing for Alzheimer's disease (AD), I compared self-referred and systematically recruited participants in a series of secondary analyses organized into three papers. Paper 1 compared the profiles of self-referred and systematically recruited participants at enrollment, finding demographic differences (e.g., fewer African Americans and greater household incomes in the self-referred cohort), and greater AD worry among self-referred participants. Cohorts did not differ on beliefs about the benefits, risks and limitations of testing, perceptions about susceptibility, severity, causes, or controllability of AD, or self-efficacy about coping, however. Paper 2 examined responses to pretest education, finding self-referred participants more likely to learn that testing was not deterministic. Analyses of test uptake found self-referred participants more likely to retain through the initial steps of the study, but no cohort differences beyond the education phase. Paper 3

examined changes to advance planning and health behaviors after testing, finding that self-referred participants with higher-risk results were more likely than their systematically recruited counterparts to report or plan changes to long-term care insurance, mental activities, diet and exercise. Self-referred participants at increased risk also reported greater uncertainty about testing results. The two groups did not differ in post-test reports of distress or positive experiences, however, or on changes to perceptions of AD susceptibility and concern. Findings suggest that individuals proactively seeking genetic susceptibility testing for common, complex diseases are more likely to follow through with testing and use it to inform behavior changes than those who are approached by others. These results highlight the challenge of generalizing findings derived from research on self-referred populations to the population at-large.

CHAPTER 1

INTRODUCTION

BEHAVIORAL RESPONSES TO GENETIC SUSCEPTIBILITY TESTING

Genetic technologies are advancing at a remarkable rate. DNA microarrays that can quickly test for hundreds of thousands of single nucleotide polymorphisms simultaneously are commonly incorporated into “multiplex tests,” and whole exome sequencing to identify mutations for rare genetic disorders has already proven to be feasible (Ng et al., 2010; Ng et al., 2009). Low-cost, whole genome sequencing appears to be on the horizon (Bonetta, 2010; Cirulli & Goldstein, 2010). These advances have facilitated the identification of genetic markers for disease and the emergence of genetic susceptibility testing.

Genetic susceptibility testing examines the DNA of healthy individuals to identify variants that predispose them to future disease. Initial approaches to genetic susceptibility testing focused on single gene testing for mutations associated with rare familial syndromes. Current approaches involve multi-locus testing for numerous common conditions. In contrast to prior testing to identify mutations with strong penetrance, the overwhelming majority of recent discoveries are genetic variants of low to moderate penetrance which increase the odds of disease by 50% at best (McCarthy et al., 2008),

and even less when combined with other traditional risk assessment strategies (Janssens & van Duijn, 2008).

Genetic susceptibility testing has generated excitement surrounding its potential to be a public health tool. The vision of many proponents is that helping individuals to identify conditions for which they have increased risk due to inherited factors will motivate them to engage in preventive behaviors (Carmona & Wattendorf, 2005; Hamburg & Collins, 2010; Hogarth, Javitt, & Melzer, 2008; Pennisi, 2007; SACGHS, 2004). For instance, an individual at increased genetic risk for Type 2 diabetes might try to lose weight, or a smoker found to be at increased risk for macular degeneration might be motivated to stop smoking. Initial findings from research on hereditary cancer syndromes were promising. Women with *BRCA1/2* mutations, which confer high risks for breast and ovarian cancer, are more likely to adhere to screening recommendations (Beery & Williams, 2007). So, too, are individuals receiving positive results on testing for Lynch syndrome, a condition where mutations confer a 70% to 80% risk for colorectal cancer (Beery & Williams, 2007). Such evidence, weighed with the existence of prophylactic strategies such as preventive mastectomies and chemoprevention with proven efficacy, have led groups such as the United States Preventive Services Task Force and the Evaluations of Genomic Applications in Practice and Prevention Working Group to recommend *BRCA1/2* testing or HNPCC testing in situations where a family or personal history of cancer is suggestive of a hereditary syndrome (EGAPP Working Group, 2009; USPSTF, 2005).

Behavioral research findings from more recent studies examining markers with lower predictive value have been mixed, however. Two randomized trials on the effects

of *L-myc* and *GSTM1* susceptibility testing, where mutations increase the risk for lung cancer among smokers, found higher short-term cessation rates among those found to be at increased risk while two studies did not (McBride, Koehly, Sanderson, & Kaphingst, 2010). Findings from work on susceptibility testing for Alzheimer's disease (AD) suggest that disclosing an increased genetic risk may motivate changes in possible AD-protective behaviors, especially addition of vitamins and nutritional supplements (Chao et al., 2008; Vernarelli et al., 2010), but no such changes were found following consumer susceptibility testing for a panel of more modifiable outcomes such as heart attacks and type 2 diabetes (Bloss, Schork, & Topol, 2011). These inconsistencies have led policymakers and opinion leaders to call for more research to better understand if and how genetic susceptibility testing can be used as a disease prevention tool (Caulfield, Ries, Ray, Shuman, & Wilson, 2010; Evans & Green, 2009; Khoury et al., 2007).

RECRUITMENT IN PSYCHOSOCIAL RESEARCH

One factor that complicates the interpretation of genetic susceptibility testing research is differences in recruitment methods. Initial research on genetic susceptibility testing focused on familial syndromes, such as hereditary breast and ovarian cancer, Lynch syndrome, and familial adenomatous polyposis. Participants of these studies were identified through research registries or oncology clinics, and targeted for recruitment primarily because of personal or family histories of disease suggestive of a strong inherited risk factor. Current studies have focused more on populations at average risk who self-refer in response to advertisements or word of mouth. Such differences may have a strong effect on the way participants respond to the studies.

Referral process is characterized in this dissertation as a spectrum of who initiated contact with potential test recipients. On one end is *systematic recruitment*. Systematically recruited participants are typically identified in lists such as research registries and health plan databases, and enrolled when providers send targeted recruitment materials. On the other end of the spectrum is *self-referral*. Self-referred participants are typically individuals who learn about genetic susceptibility testing research through media, the Internet, or word of mouth and enroll only after initiating contact with the test provider. An important limitation of studies that rely upon self-referred participants is an inability to characterize people who declined to participate. Depending on the study aims and the kinds of inferences that need to be made, though, both types of referral processes can introduce biases.

Differences in referral processes affect the profiles of the samples enroll in health research. An analysis of a bipolar disorder disease registry found that patients who self-referred were better educated and more likely to be married than participants who learned about the registry through other means, including physician referrals (Scholle et al., 2000). An examination of a diet and exercise intervention for cancer survivors found that self-referred participants had lower fruit and vegetable consumption than those enrolled through a registry (Snyder et al., 2008). Self-referred populations are typically more likely to engage in an intervention, too, whether it involves genetic testing (Roberts et al., 2004) or smoking cessation (McBride et al., 1998).

They may be more likely to report behavior changes afterwards, also (McBride et al., 1998), although findings from meta-analyses have shown mixed results (Tzelepis, Paul, Walsh, McElduff, & Knight, 2011). Differences may involve more than a greater

readiness to make changes among self-referred individuals. In a randomized trial to improve diet and exercise among cancer survivors, for instance, 28% of the intervention arm achieved the exercise goal compared to 12% of the control arm when examining only systematically recruited participants. When examining self-referred participants, however, only 22% of the intervention arm achieved the exercise goal compared to 25% of the control arm. Similar percentages were noted on dietary outcomes (Snyder et al., 2008). Although interaction effects were not explicitly analyzed, the results suggest two important points: (a) self-referred participants may be more likely to change health behaviors than systematically recruited participants, regardless of the intervention; and (b) health behavior interventions may be more effective for systematically recruited participants than self-referred ones.

GOAL AND ORGANIZATION OF DISSERTATION

The overall goal of this dissertation is to understand the implications of different sampling strategies for genetic susceptibility testing research by examining self-referred versus systematically recruited populations. In Chapter 2, I summarize the literature on genetic susceptibility testing, with a focus on psychosocial factors that may differ between self-referred and systematically recruited participants at the time of enrollment. In Chapter 3, I present the conceptual model I used as the foundation of this dissertation, one that tries to explain cohort differences in test uptake and behavioral responses to test results.

The next three chapters present the analyses I conducted for this dissertation. Chapter 4 investigates how self-referred and systematically recruited participants differ at

enrollment, detailing demographic, psychological, and affective differences. The aims and hypotheses for Chapter 4 are:

Specific Aim 1: To describe how the study population enrolled through self-referral differs from the study population enrolled through systematic recruitment on testing beliefs, behavioral beliefs, illness perceptions, and emotions.

Hypothesis 1a: Self-referred participants are more likely to be female, Caucasian, younger, of higher socioeconomic status, and have stronger family histories of AD than systematically recruited participants.

Hypothesis 1b: Self-referred participants have stronger beliefs about the benefits of testing, the efficacy of health behaviors to prevent AD, greater perceived susceptibility to AD, stronger beliefs that genetics causes AD, and greater coping self-efficacy than systematically recruited participants.

Hypothesis 1c: Self-referred participants have greater pretest AD concern and worry than systematically recruited participants.

Chapter 5 summarizes how self-referred and systematically recruited participants responded to pretest education, and also tests whether self-referred participants were more likely to follow through with testing than systematically recruited participants. Self-referral may increase uptake rates of testing because self-referrers are more likely to have characteristics associated with greater test uptake (e.g., intrinsic motivation) than those identified through systematic recruitment. In addition, the use of self-referral rather than systematic recruitment processes may affect the way pre-test education changes

cognitions and motivation to follow through with testing. The aims and hypotheses for Chapter 5 are:

Specific Aim 2: To understand the implications of different referral processes on test uptake and its determinants.

Hypothesis 2a: Self-referred participants in the REVEAL Study are more likely to report changes to AD susceptibility perceptions than systematically recruited participants after pretest education.

Hypothesis 2b: Self-referred participants are less likely to drop out of the REVEAL Study prior to genetic risk disclosure than systematically recruited participants.

Chapter 6 delves into responses to the genetic risk estimates, testing whether self-referred participants were more likely to make or plan changes to advance planning and health behaviors than systematically recruited participants. Chapter 6 also assesses psychological responses that may explain differences in behavioral outcomes. Specific aims and hypotheses for Chapter 6 are:

Specific Aim 3: To understand the implications of different referral processes on post-test changes to a) advance planning and b) health behaviors.

Hypothesis 3: Self-referred participants are more likely to report changes and intentions to change advance planning, use of dietary supplements, and mental activities than systematically recruited participants, after controlling for *APOE* genotype.

Secondary Hypothesis 3a: Self-referred participants are more likely to discuss AD preventative measures during genetic risk disclosure than systematically recruited participants, after controlling for *APOE* genotype.

Secondary Hypothesis 3b: Self-referred participants are more likely to expect testing to aid in decision making and provide reassurance than systematically recruited participants.

Secondary Hypothesis 3c: Self-referred participants are more likely to report changes from baseline to AD control beliefs and susceptibility perceptions after testing than systematically recruited participants, after controlling for *APOE* genotype.

Secondary Hypothesis 3d: Self-referred participants are more likely to report changes from baseline to a) AD concern and worry after testing, as well as b) stronger negative and positive emotional responses to disclosure, than systematically recruited participants, after controlling for *APOE* genotype.

Finally, Chapter 7 summarizes findings from these individual analyses, discusses themes that emerged between them, addresses the theoretical implications of dissertation findings, and introduces areas for future research.

This dissertation improves understandings about how sampling strategies affect uptake of and behavioral responses to genetic susceptibility testing, and provides insight about the different ways self-referred and systematically recruited participants of genetic susceptibility testing research respond to pre-test education and results disclosure. The analyses from this dissertation have important implications with respect to generalizing the findings from existing research on genetic susceptibility testing to the population at-large.

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CHAPTER 2

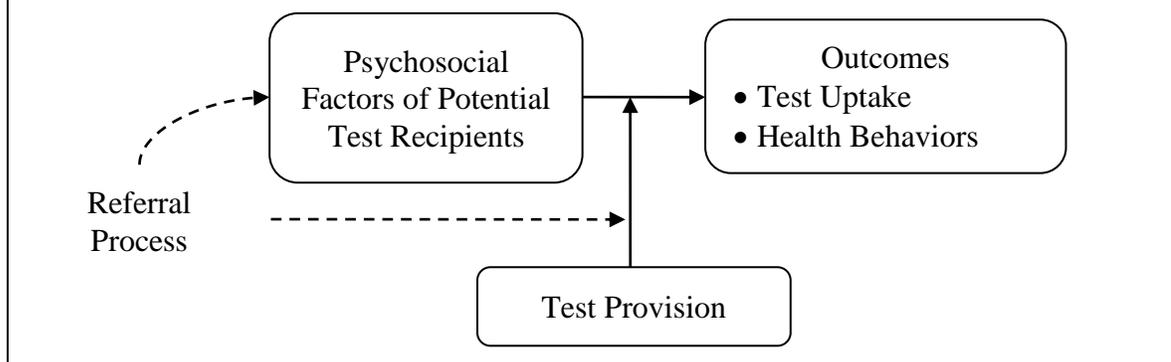
LITERATURE REVIEW

This chapter reviews important factors that self-referred and systematically recruited participants may differ on, factors that may explain differences in rates of test uptake and psychosocial responses to test results. It also reviews factors that may not vary by referral process, but still have a critical impact on outcomes of interest. It is divided into two subsections: (1) factors related to research participants and genetic test seekers, and (2) factors related to genetic test provision, including genetic risk communication. The intent of the literature review is to address the following questions:

- a) What theoretical mechanisms and empirical evidence justify the importance of each factor with respect to enrollment in genetic susceptibility testing research, uptake of testing, or behavioral responses to genetic susceptibility information?
- b) How does the context of genetics affect how we should think about these factors and interpret existing evidence?
- c) What is the impact of different referral processes on these factors?

A model to orient this review is presented in Figure 1. Referral processes determine the characteristics of a research population, and outcomes of interest – uptake

Figure 1. Overarching model to orient the literature review.



of testing and changes to health behaviors – are conceptualized to be primarily a function of test recipient factors. These test recipient factors are assumed to be affected by information in the form of pre-test education and results from a genetic risk assessment provided by a genetic test provider. The implications of different referral processes are addressed in the discussion of each factor as well as in a section that presents a more detailed conceptual model that describes the relationships among the constructs of interest.

The literature review that follows is organized according to this model. It first focuses on individual-level factors of potential test recipients, including those more fixed in nature (e.g., demographic factors, dispositional factors, genetic/health literacy, social support) and those that are likely to be altered by communications (e.g., cognitions related to testing, behaviors, and diseases; and emotions). The literature review then addresses factors related to test provision, including institutional characteristics (e.g., setting and training) and the communication of information (e.g., pre-test education, disclosure of genetic risk information). These components are used as building blocks for the conceptual model presented in Chapter 3 to predict enrollment, uptake of genetic susceptibility testing and behavior changes in response to test results.

FACTORS OF POTENTIAL TEST RECIPIENTS

This section addresses demographic, dispositional, and psychosocial factors that may vary by referral process and may be important determinants of test uptake and subsequent health behavior changes.

Demographics

Systematic recruitment may be considered a form of outreach, one that favors those who might otherwise not self-refer to research. I draw from the literature on research disparities to make inferences about the populations that self-referral favors and those that systematic recruitment favors.

Gender

Women appear to be more interested in genetic susceptibility testing research than men, a trend that differs from the trend in more general health research. Overall, men are more likely than women to participate in health research, whether the focus is on clinical trials for cancer (Giuliano et al., 2000; McQuillan, Porter, Agelli, & Kington, 2003; Murthy, Krumholz, & Gross, 2004) or on identifying genetic risk factors for disease (Ford et al., 2006; Murthy et al., 2004). Data from psychosocial research on genetic susceptibility testing show the opposite trend: women tend to have stronger positive beliefs about genetic testing in studies of genetic testing for colorectal cancer and AD risk (Esplen et al., 2007; Roberts, LaRusse, et al., 2003). Such differences are reflected in study recruitment and retention. A nuanced analysis was conducted on data from the Multiplex Initiative, a study that examined interest in and responses to multi-gene susceptibility testing for multiple diseases sampled from insured patients of the Henry Ford Health System in the Detroit metro area. By taking a three stage population-based

approach, the Multiplex Initiative allowed for inferences to be drawn about the impact of gender on (1) participation in psychosocial research about health, (2) interest in genetic susceptibility testing, and (3) uptake of susceptibility testing. In this study, women were more likely than men (39% vs 29%) to complete a telephone survey about factors affecting health and subsequently more likely to log onto a website to learn more about susceptibility testing (34% vs 29%). Once informed, though, gender was non-predictive of uptake of genetic testing (Alford et al., 2011).

The data from the Multiplex Initiative, a study using systematic recruitment, suggest that systematic recruitment enrolls more women than men, but both genders are equally likely to follow through with testing once pre-test education is complete. Given the greater “barrier to entry” self-referral strategies impose, it’s likely that self-referral attracts those with stronger motivations to be tested and skew enrollment disparities further.

Race and ethnicity

Racial and ethnic minorities tend to be less likely to participate in genetic susceptibility testing research than whites. In the aforementioned Multiplex Initiative, whites were more likely than African Americans to complete an initial telephone survey (36% vs 33%), seek additional information about genetic susceptibility testing (40% vs 26%), and follow through on actual testing (55% vs 30%) (Alford et al., 2011). Such disparities are consistent with disparities in clinical trial research in general. Numerous studies have documented differences between whites and non-whites - particularly African Americans - in areas such as genetic epidemiological research (McQuillan et al., 2003), cancer epidemiology (Ford et al., 2006), and cancer clinical trials (Murthy et al.,

2004). Assuming that research disparities parallel those we might expect between self-referred and systematically recruited populations, the evidence suggests that recruitment strategies that encourage self-referral attract fewer minority participants.

The abovementioned disparities do not seem to be the results of unfavorable attitudes about genetic susceptibility testing. Studies on breast/ovarian cancer genetic testing, for instance, have found that African Americans and Latinos from high-risk families have comparable to more positive beliefs about genetic testing relative to whites (Donovan & Tucker, 2000; Hughes et al., 1997; Ramirez, Aparicio-Ting, de Majors, & Miller, 2006). In addition, black Americans and Latinos appear to have more favorable attitudes about genetic testing than Caucasians, particularly for conditions considered untreatable (Singer, Antonucci, & Van Hoewyk, 2004), although attitudes about genetic testing for AD risk were less positive and knowledge about the topic was lower among African Americans than Caucasians (Hipps, Roberts, Farrer, & Green, 2003). Substantial differences in sampling strategies exist between these studies, complicating interpretation of the data. What the evidence suggests, though, is that black Americans don't appear biased against specific types of genetic testing compared to whites.

More important drivers of ethnic and racial disparities in genetic susceptibility testing research are likely to be the same kinds of barriers that contribute to disparities in clinical medical research in general, including strained relationships with researchers and medical professionals, disproportionate access to logistical resources such as transportation, and poor community relations, to name just a very few issues (Wells & Zebrack, 2008). Low trust of researchers and medical institutions may be particularly important barriers to participation for marginalized populations such as Latinos and

African Americans, given how the “objectivity” of science has many times been used as a basis to promote programs harmful to minority communities (Caplan, 1992; Jackson, 1999; Markel, 1992; Pernick, 1997) and given how even the most promising health research findings that seem to benefit some groups may be tainted by ulterior motives, such as protecting patent rights on medications (Kahn, 2003, 2006). Black Americans are more likely than white individuals to see genetic research in general as harmful to society (Furr, 2002; Thompson, Valdimarsdottir, Jandorf, & Redd, 2003) and are more skeptical about media coverage about genetic findings (Tambor, Bernhardt, Rodgers, Holtzman, & Geller, 2002). Similar distrust of genetic research and the medical system have been found among Latinos (Thompson et al., 2003).

Age

The impact of age on genetic testing decisions and responses to testing appears weaker than many commentators expect. The ability of most prevention strategies to reduce disease risk is greatest when individuals are younger (Safer, 1982). Moreover, genetic tests are increasingly available on the Internet (Geransar & Einsiedel, 2008; Janssens et al., 2008), a medium where younger individuals are more comfortable (Couper et al., 2010; Large, 2005; Pew Internet & American Life Project, 2005). Age does not appear to have a strong effect on attitudes about genetic testing, though. Older individuals, for example, reported more favorable attitudes than younger individuals about genetic testing in two studies about hereditary breast cancer testing (Donovan & Tucker, 2000; Kessler et al., 2005) as well as in DTC genetic testing (Bloss et al., 2010), and a national survey of adults in Britain found the greatest interest in testing for heart disease and cancer risk among those in middle age adults (ages 46-60) (Sanderson,

Wardle, Jarvis, & Humphries, 2004). In fact, how individuals adopt new technologies is generally not a function of age (E. M. Rogers, 2003). How age affects decisions about genetic susceptibility testing may have more to do with the typical age of disease onset.

Self-referral appears to favor younger adults, though. Younger individuals, particularly those under the age of 65, are more likely to participate in clinical trials than older adults (Hutchins, Unger, Crowley, Coltman Jr., & Albain, 1999; Lewis et al., 2003; Murthy et al., 2004); and in a randomized trial assessing the effectiveness of a self-help binge-eating intervention, self-referred participants were younger than systematically recruited participants (DeBar et al., 2009). In addition, a comparison of self-referred and registry-ascertained participants in a diet and exercise intervention for cancer survivors found that self-referred participants were younger than their counterparts (Snyder et al., 2008).

Income and education

Individuals with more education and higher economic status tend to be earlier adopters of new technologies (E. M. Rogers, 2003). Such trends are reflected in numerous studies about genetic susceptibility testing. Household income has been shown to be associated with fewer perceived negative outcomes (Donovan & Tucker, 2000) and a greater awareness of genetic testing for hereditary breast and ovarian cancer risk (Honda, 2003). Demographics of individuals seeking genetic susceptibility testing for AD are skewed towards those with greater incomes and high education (Roberts et al., 2004); and in the aforementioned Multiplex Initiative, individuals from neighborhoods with higher educational attainment were slightly more likely to complete the baseline telephone survey than those from neighborhoods with lower attainment (35% vs 32%).

Interestingly, education did not predict additional information seeking about genetic susceptibility testing or uptake of actual testing in the Multiplex Initiative (Alford et al., 2011), and a nationally representative survey found greater education to be associated with *lower* willingness to pay for testing for many chronic conditions (Neumann et al., 2012). It is possible that more educated individuals better recognize the limited predictive value of those types of tests.

It is well-recognized that the populations enrolled in clinical trials also tend to be skewed towards those of high socioeconomic status (Baquet, Commiskey, Daniel Mullins, & Mishra, 2006; Sateren et al., 2002), a point that suggests that self-referral methods favor those of higher income and educational attainment.

Personal and family history of disease

Although genetic susceptibility testing is intended to provide healthy individuals with assessments of risk for future disease, the lines between health and illness are often blurry. Diagnostic criteria for type 2 diabetes, for example, includes fasting plasma glucose and HbA_{1c} cut points where frequencies of complications such as retinopathy increase, but individuals just below cutoff are often diagnosed as having pre-diabetes or hyperglycemia (Kirkman & Kendall, 2011). Similarly, individuals with mild memory problems may be diagnosed as having mild cognitive impairment rather than AD (Morris, 2006). This issue is gaining importance given expanding efforts to identify individuals in a presymptomatic state of disease (de Ruijter et al., 2009; Dubois et al., 2010).

Such distinctions are important because a personal history of disease can affect responses to genetic susceptibility test results. For instance, cancer-free patients often respond as they anticipate, but patients with cancer often have stronger emotional

responses than they expected (Coyne, Kruus, Racioppo, Calzone, & Armstrong, 2003; Dorval et al., 2000). By extension, we might expect stronger emotional responses to genetic susceptibility testing among those whose health may suggest an undiagnosed condition or sub-clinical disease state.

Evidence suggests that adults with disease are often are harder to reach initially, but once reached, are more likely to participate in research (Moorman, Newman, Millikan, Tse, & Sandler, 1999). In a randomized trial assessing the effectiveness of a self-help binge-eating intervention, self-referred participants had more bingeing and eating problems than systematically recruited participants (DeBar et al., 2009). In addition, self-referred participants who met trial eligibility criteria had more body image concerns than those enrolled through outreach (DeBar et al., 2009). A comparison of self-referred and registry-ascertained participants in a diet and exercise intervention for cancer survivors found that self-referred participants were more likely to have had later-stage disease and had lower rated quality of life than those enrolled through a registry (Snyder et al., 2008). An analysis of self-referred versus population-sampled registry members found self-referred participants to have much stronger personal histories of cancer, but were otherwise similar demographically (Henrikson, Harris, & Bowen, 2007), and self-referred participants in a bipolar disease registry tended to have more hospitalizations who enrolled through other means (Scholle et al., 2000). The evidence suggests that self-referred participants enroll with more health problems than systematically recruited participants.

Family history has received more attention in the area of genetic susceptibility testing. Systematic reviews of genetic susceptibility testing for breast cancer have found

that individuals with a family history of disease have over twice the odds of following through on testing than those without (Ropka, Wenzel, Phillips, Siadaty, & Philbrick, 2006). In addition, family history of disease often affects how individuals practice disease prevention, and individuals who have close relatives affected by a condition often have greater susceptibility perceptions (Lerman et al., 1996). Family history is also associated with preventive behaviors. Having a relative affected with melanoma, for instance, has been associated with greater rates of skin self-exams: 72% of first degree relatives of melanoma patients performed at least one within the previous year compared to 15% of the general public (Berwick, Begg, Fine, Roush, & Barnhill, 1996; S. Manne et al., 2004). Family histories of disease can have ‘spillover’ effects on risk perceptions of other types of cancer, too. Individuals with family histories of breast cancer, for instance, often have higher susceptibility perceptions about other types of cancer (Rubinstein et al., 2011). Self-referral is likely to enroll populations with stronger family histories of disease than systematic recruitment. An analysis of self-referred versus population-sampled registry members, for instance, found self-referred participants to have much stronger family histories of cancer than population-based participants (Henrikson et al., 2007).

Dispositions / Personality Traits

Dispositions and personality traits are important determinants of how individuals seek and respond to health information. A comparison of self-referred and registry-ascertained participants in a diet and exercise intervention for cancer survivors found that self-referred participants were more likely to report “fighting spirit” coping styles than those enrolled through a registry (Snyder et al., 2008); but in general, how referral processes affect the dispositional profile of genetic susceptibility testing study samples

has not been examined. In addition, how dispositional traits are associated with testing that uses markers with lower predictive power is also unclear. The Multiplex Initiative found that disposition towards general health information seeking was unassociated with the likelihood of attempting to learn more about testing or uptake of testing (McBride et al., 2008). Other dispositional traits were not examined. Findings presented here are drawn almost exclusively from the literature on genetic susceptibility markers with strong predictive power.

Monitoring and *blunting* dispositions are popular characterizations of how individuals respond to threatening information, such as disclosure of genetic susceptibility test results (Miller, 1992, 1995). Monitors tend to seek as much information as possible and have higher levels of perceived risk and worry, whereas blunters often ignore or suppress thoughts about stressors. In a study assessing the impact of an telephone intervention to educate women about breast cancer genetic testing, high monitors were found to learn more during calls to an information service and have greater changes in perceived risk than low monitors (Miller et al., 2005). High monitors are more likely to want more information and to desire greater involvement with decision-making about genetic testing (Wakefield, Homewood, Mahmut, Taylor, & Meiser, 2007). They also report greater depression and anxiety following amniocentesis (Croyle & Lerman, 1995). In contrast, blunters tend to want less information, and have been found to have weaker understandings of their family histories of disease (Kelly et al., 2007).

Need for cognition, a related concept, is a stable personality trait that refers to “an individual’s tendency to engage in and enjoy effortful cognitive endeavors” (Cacioppo, Petty, Feinstein, & Jarvis, 1996, p. 197). In general, people who are high in need for

cognition are more likely to be persuaded by argument strength while those who are low in need for cognition are more likely to be persuaded by whether or not they consider the information source to be credible (Bakker, 1999; Cacioppo & Petty, 1982; Cacioppo, Petty, Feinstein, & Jarvis, 1996). Need for cognition has not been examined in the context of genetic susceptibility testing, but is likely to play a key role in how genetic susceptibility test results are interpreted.

Dispositional *optimism* and *pessimism* is another trait frequently examined in genetic susceptibility testing research. A population-based study of residents of Vermont, New Hampshire, and Maine found optimism to be associated with greater intentions to seek genetic testing for colon cancer risk, with their impact mediated by decreases in perceptions of disease susceptibility and increases in perceived benefits of testing (Bunn, Bosompra, Ashikaga, Flynn, & Worden, 2002). In addition, the study showed greater pessimism to also be associated with greater intentions to seek testing, with increases in perceived barriers but also increases in perceived benefits. Similarly, a telephone interview of adults in upstate New York found an association between dispositional optimism and pessimism and willingness to undergo genetic testing through pathways mediated by disease susceptibility perceptions and barrier perceptions (Bosompra, Ashikaga, Flynn, Worden, & Solomon, 2001). While dispositional optimism and pessimism has not been examined in the context of genetic susceptibility testing, it is likely that those with greater levels of optimism are more likely to follow through on genetic susceptibility testing and will respond more positively to indications of increased genetic risk.

Given the level of sophistication associated with the way genetic susceptibility tests are currently offered, one might assume that self-referral favors information monitors, individuals who are high in need for cognition, and those with optimistic dispositions. Such suppositions have not been tested, however.

Health/Genetic Literacy

Genetic susceptibility information is complicated, and the way such services are currently presented does not facilitate understanding. DTC genetic testing company websites, for instance, have been found to be written at a grade 15 education level (Lachance, Erby, Ford, Allen, & Kaphingst, 2010). In contrast, data from the National Adult Literacy Survey showed that over 20% of Americans had limited literacy skills, and another 25% demonstrated difficulty with higher level reading and problem solving skills (Kirsch, Jungeblut, Jenkins, & Kolstad, 2002). The ability of most Americans to be able to understand information provided by genetic susceptibility testing providers is a serious concern (McBride, Bowen, et al., 2010; McBride, Koehly, Sanderson, & Kaphingst, 2010).

In particular, health literacy has received much attention. Health literacy was defined in *Healthy People 2010* as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions” (U.S. Department of Health and Human Services, 2010, p. iii). An IOM expert panel identified four major domains of health literacy: (1) cultural and conceptual knowledge, (2) oral literacy, including speaking and listening skills, (3) print literacy, including writing and reading skills, and (4) numeracy (Baker, 2006). Genetic susceptibility testing, and genetic services in general, push the limits on all these

domains. Information provided by genetic susceptibility tests are rarely definitive, and individuals making decisions about and interpreting results of genetic susceptibility testing are required to process probabilistic rather than definitive information, understand and communicate implications for relatives in addition to themselves, to name just a few tasks. Thousands of articles have addressed the topic of health literacy. This review addresses a dimension of particular relevance to genetic susceptibility testing: genetic literacy.

Among the greatest challenges to the incorporation of genetic susceptibility testing into health promotion is the limited genetic literacy of the public. Policymakers, medical professionals and academics frequently voice concern about the American public's understandings about genetics (Griffiths, 1993; Kegley, 2003; SACGHS, 2004; Wang, Bowen, & Kardia, 2005). They have good reason. Most Americans are familiar with elementary genetic language and have a general comprehension of terms such as "genes" and "heredity" (Lanie et al., 2004; National Science Board, 2008), but become frustrated or hesitant when they try to explain basic concepts such as how genes work, how they are passed along or where they are located in the body (Emslie, Hunt, & Watt, 2003; Lanie et al., 2004). Surveys also show that Americans overestimate the capabilities of genetic services, believing that tests for qualities such as intelligence and technologies such as gene therapy are currently being used (Genetics and Public Policy Center, 2004; Singer, Corning, & Lamias, 1998). Those who seek genetic services have the same sorts of misunderstandings, scoring little better than random chance on knowledge assessments on a wide array of scales (Scheuner, Sieverding, & Shekelle, 2008; Walter, Emery,

Braithwaite, & Marteau, 2004). By any measure, genetic literacy among the U.S. public is poor.

Genetic literacy has no standardized definition, although many have been proposed. Some definitions are health-centered (McInerney, 2002) while others encompasses social as well as healthcare-specific knowledge (Bowling et al., 2008; Institute of Medicine, 1994). Many experts argue that important and distinct dimensions of genetic literacy exist, such as an awareness of the capabilities of genetic services, the relationship between genes and disease, the mechanisms of genetic inheritance, and the social implications of genetic advances (Hott et al., 2002; Richards, 1996; Smerecnik, Mesters, de Vries, & de Vries, 2008). How each of these forms of knowledge affect decision-making about genetic services or responses to genetic susceptibility information has not yet been examined.

Family history, race and ethnicity are important determinants of genetic understandings. Understandings about genetics tend to be crafted from family and kin narratives with strong social-group bases (B. R. Bates, 2005; Emslie et al., 2003; Lanie et al., 2004; Richards, 1996). Such narratives are often based in lay theories about genetics that equate physical similarities with genetic similarities (Emslie et al., 2003; Richards, 1996; Shepherd, Hattersley, & Sparkes, 2000). As a result, understandings can vary greatly between ethnic groups. Some Native Americans, for instance, make no distinction between blood relatives and non-blood relatives (Tsosie, 2007).

Of the studies exploring ethnicity and/or gender differences, some show poorer awareness among black Americans about cancer genetics and awareness about the capabilities of genetic tests (Donovan & Tucker, 2000; Lerman et al., 1996; Singer et al.,

2004). However, evidence suggests that while African Americans may be less knowledgeable about the physiological aspects of genetics, such as how different parts of the body carry the same genes, they may be more sensitive towards the social implications of genetics, such how racial disparities are misattributed to inherited differences (Christensen, Jayaratne, Roberts, Kardia, & Petty, 2010; Sheldon, Jayaratne, Feldbaum, DiNardo, & Petty, 2007). Gender also plays an important role, where women seem to understand the social implications of genetics better (Christensen, Jayaratne, et al., 2010; Siegrist, 2000). Such assertions are supported by qualitative research finds that women are more likely than men to mention the words “genes” and “genetics” as an explanation of inheritance (Stacey, 1996).

Depending on how genetic literacy is defined, it is likely that individuals who self-refer to genetic susceptibility testing will have higher levels than those who are systematically recruited. In addition, the abovementioned data demonstrates that demographic factors have an important relationship with genetic literacy. If sample profiles differ demographically by referral process, then so will genetic literacy levels.

Testing Beliefs

Beliefs about how decisions satisfy perceived needs are central to many theories of decision-making and behavior. This section addresses beliefs about genetic testing divided into two themes: perceptions about the benefits, risks and limitations of testing; and beliefs that testing can reduce uncertainty.

An important caveat of this section is that information needs evolve during information seeking (M. J. Bates, 1989). Said another way, what information needs test recipients hope to satisfy at the beginning of the testing process may evolve through the

process. Genetic counseling has been shown to change how individuals change their ratings of the benefits of genetic susceptibility testing for hereditary breast and ovarian cancer (Lerman et al., 1997), and a comparison of pre-test and post-test reasons for seeking genetic susceptibility testing for AD found that individuals rated benefits related to prevention, treatment, and planning long-term care lower after testing, but didn't change ratings of the benefits related to emotional outcomes or curiosity (Christensen, Roberts, Uhlmann, & Green, 2011). If genetic susceptibility testing is a goal-directed behavior, these data suggest that the goal may evolve as test recipients progress from establishing contact with test providers to receiving pre-test education to results disclosure and beyond.

Perceived benefits, risks and limitations

Perceived benefits, risks and limitations are central constructs in many popular theories of health behavior such as the Health Belief Model (Rosenstock, 1974) and the Transtheoretical Model (Prochaska, Redding, & Evers, 2008). They have received much attention in the area of genetic susceptibility testing, and are strong predictors of interest, intent, and follow through on genetic susceptibility testing (Kasparian, Meiser, Butow, Simpson, & Mann, 2009; Lerman et al., 1996; Roberts, 2000; Roberts, Connell, et al., 2003).

The benefits, risks and limitations individuals perceive in genetic susceptibility testing often vary by demographic factors. Women, as mentioned earlier, have reported more benefits to testing than men for conditions such as colorectal cancer and AD (Espen et al., 2007; Roberts, LaRusse, et al., 2003), as do people with higher risk perceptions and personal histories of disease (Kessler et al., 2005). Black Americans have

reported more benefits than whites in genetic testing for conditions such as familial breast cancer (Donovan & Tucker, 2000; Hughes et al., 1997; Singer et al., 2004), but fewer benefits for conditions such as AD (Hipps et al., 2003). Conversely, they also have reported greater risks and limitations for familial breast cancer (Donovan & Tucker, 2000; Hughes et al., 1997). Less educated individuals also perceive fewer benefits (Donovan & Tucker, 2000).

Although often treated in analyses as a one-dimensional construct, the importance of some benefits are more predictive of test uptake than others. Among women who have already had breast and/or ovarian cancer, for instance, benefits related to prevention and early disease detection tend to be more predictive of intent to test than other reasons (Bluman et al., 1999; Cappelli et al., 1999), but other benefits had important predictive power, too, especially those related to gaining knowledge and informing the family. For example, providing information for family members or preparing them for disease was consistently one of the most important predictors of seeking genetic susceptibility information (Armstrong et al., 2000; Cappelli et al., 1999; Christensen, Roberts, Shalowitz, et al., 2011; Roberts, LaRusse, et al., 2003; Vernon et al., 1999). The most commonly endorsed reason for wanting genetic testing for hereditary breast and ovarian cancer was to learn if one's children were at risk (Struewing, Lerman, Kase, Giambarresi, & Tucker, 1995), even though presymptomatic testing of children is generally not recommended except for a few genes with well-characterized, highly penetrant mutations where risk reduction strategies exist (Borry, Goffin, Nys, & Dierickx, 2008; Borry, Stultiens, Nys, Cassiman, & Dierickx, 2006).

Perceptions of risks and limitations of testing are also important predictors of testing decisions. Risks and limitations include the possibility of worry and distress about self and/or children's risks for disease, stigmatization, and potential discrimination in employment and insurance. In fact, fears about discrimination are among the most powerful predictors of declining testing (Armstrong et al., 2000; Armstrong, Micco, Carney, Stopfer, & Putt, 2005; Oster et al., 2008; Thompson et al., 2002). While perceptions may be different now given the passage of the Genetic Information Nondiscrimination Act of 2008 (GINA), a federal law prohibiting the use of genetic susceptibility information by employers and health insurers, a patchwork of state legislation has long existed, and other types of protection like long-term care and disability insurance are not covered by GINA (Hudson, 2007). Moreover, the possibility exists that GINA may have unintended consequences by making stigmatization and discrimination based on lifestyle factors more acceptable (Van Hoyweghen & Horstman, 2008). How GINA affects discrimination fears will be a subject of ongoing importance.

Perceived benefits, risks and limitations may also predict behavioral responses to testing. It should be noted that although disease prevention may be the most important criterion for judging the utility of genetic susceptibility testing among physicians, policymakers, and payers, it may not be the goal of test recipients. People who seek genetic susceptibility tests cite myriad reasons for doing so, including to relieve worry about disease risk, financial planning and simple curiosity (Lerman, Seay, Balshem, & Audrain, 1995; Roberts, LaRusse, et al., 2003). Reduction of disease risk is only one of many reasons a person may undergo a susceptibility test, and only one of many responses to susceptibility testing. Indeed, given the limited predictive value of most current genetic

susceptibility tests and their general inability to provide information that would change prevention strategies, the inability of genetic susceptibility testing to motivate health behavior change in many situations is not surprising.

It is probable that participants who self-refer to genetic susceptibility testing do so precisely because they perceive the benefits of testing to outweigh the risks and limitations, although evidence to support this assertion is currently lacking.

Reduction of uncertainty and curiosity

Genetic testing as a form of information seeking behavior has long received attention, and curiosity and “just want to know,” when queried, are commonly-endorsed reasons individuals cite for interest in genetic susceptibility testing (Makeeva, Markova, Roses, & Puzyrev, 2010; Roberts, LaRusse, et al., 2003; Struewing et al., 1995). In fact, a stronger desire to know more about one’s personal genome was one of the best predictors of willingness to undergo genetic susceptibility testing in a population-based study conducted in Russia (Makeeva et al., 2010).

These goals likely reflect desires to reduce uncertainty. Uncertainty is an aversive state, and desires to reduce it often motivate individuals to seek genetic susceptibility testing. Individuals may pursue genetic susceptibility testing to understand their chances of developing illness (e.g., am I at risk for breast cancer or not?), to increase their certainty about what their chances of disease actually are (e.g., I am certain I have a 1 in 8 chance of developing breast cancer vs I think I have a 1 in 8 chance of developing breast cancer), or to differentiate the importance of different risk factors (e.g., environmental vs genetic) and prevention strategies (e.g., lifestyle modification or medications), among other reasons. To help healthcare providers recognize sources of

uncertainty and develop appropriate strategies for reducing it or helping patients cope with it, researchers have developed taxonomies that delineate forms of uncertainty from the patient and layperson perspective. Some approaches have focused on the nature of the uncertainty, distinguishing between information complexity, information comprehensiveness, probabilistic uncertainties, information coherence, and individual beliefs (Babrow, Kasch, & Ford, 1998). Others have identified dimensions of uncertainty according to processes, distinguishing between its implications for tasks such as diagnosis and prognoses, life changes, and treatment (Kasper, Geiger, Freiburger, & Schmidt, 2008).

A system proposed by Han, Klein and Arora is used here. They propose a three-dimensional taxonomy for uncertainty based on its source, the substantive issue, and its locus. They distinguish source according to uncertainty about the likelihood of outcomes such as disease onset (probability), uncertainty about the validity of information such as risk estimates (ambiguity), and uncertainty stemming from the overlapping implications of information with respect to understanding causes, outcomes, and effects (complexity). Substantive issue refers to the scientific, practical, or personal concerns implications of information with respect to illness. Examples of these concerns include whether the information pertains to diagnoses, prognoses, treatments, how to seek care, or interpersonal relationships. Lastly, locus refers to where the uncertainty resides, including patients, clinicians, both, or neither (Han, Klein, & Arora, 2011). This document focuses on uncertainty related to the substantive issue of disease susceptibility with a locus of the potential genetic susceptibility test recipients, and will differentiate between types of

source uncertainty. However, other types of uncertainty will be addressed throughout where appropriate, particularly at the locus of the test provider.

The desire to reduce probability uncertainty about the potential onset of disease uncertainty (referred to as *uncertainty about health*, henceforth) is a powerful reason many people cite for seeking genetic susceptibility testing. Nearly 40% of individuals with a 50/50 chance of inheriting a Huntington's disease mutation who responded to a mailed survey asserted that their main reason for wanting testing was to end uncertainty in their lives (Mastromauro, Myers, Berkman, Opitz, & Reynolds, 1987). Similarly, nearly 60% of colorectal cancer survivors surveyed about their attitudes about HNPCC testing found that increased certainty of risk was an important motivator for seeking testing (Espen et al., 2007). A questionnaire presenting a series of hypothetical scenarios and administered to a convenience sample found greatest interest in testing scenarios where predictive power was greatest (Barnoy, 2007), and a study of perceptions about testing for Lynch Syndrome among a cohort with a strong family history of disease, for instance, concluded that, "the predominant motive behind genetic testing was to obtain certainty, irrespective of the result" (M. Keller et al., 2002, p. 297). Consistently, the desire to reduce uncertainty about health predicts uptake of testing.

This reason for pursuing testing is inherently problematic, though. Genetic susceptibility testing, by definition, *never* provides definitive information about developing or avoiding disease, meaning this type of uncertainty will never be resolved objectively by testing. In this respect, learning about the limited positive and negative predictive value of genetic susceptibility test results likely decreases the motivation of most individuals to seek and follow through with it, and particularly among those who

sought testing to reduce uncertainty about onset specifically. About half of individuals considering genetic susceptibility testing for breast cancer, colon cancer, and bipolar disease have cited the inability of testing to provide definitive answers about risk as an important reason not to pursue testing (Jacobsen, Valdimarsdottier, Brown, & Offit, 1997; Kinney et al., 2001; S. L. Manne et al., 2007; Meiser et al., 2008).

Uncertainty about the validity of risk estimates (referred to *risk ambiguity*, henceforth) represents a second source of uncertainty that is likely to be an important reason individuals undertake genetic susceptibility testing. Individuals may perceive themselves to be at greater or lesser risk for disease while simultaneously recognizing that they have no basis for their perceptions. Genetic susceptibility testing is a mechanism for these individuals to refine their self-assessed risk for disease in a way that they perceive has strong credibility, and evidence has shown that risk information derived through genetic testing has greater influence on perceptions such as disease threat than more established risk-assessment strategies such as family health history analysis (Janssens et al., 2008; LaRusse et al., 2005). These effects occur despite persistent concerns about the validity of many genetic risk markers (Janssens et al., 2008) and the way numerical risk estimates are developed, when numerical estimates are provided. Like uncertainty about health, the desire to reduce risk ambiguity appears to be a strong predictor of test uptake. Qualitative work with a sample of Australians found understanding risk with more accuracy to be one of the most commonly cited reasons for considering genetic testing for familial melanoma (Kasparian, Meiser, Butow, Soames Job, & Mann, 2007).

Although many recommendations have been made regarding the communication of risk information (e.g., personalizing and contextualizing information to increase meaning to recipients, tailoring presentation styles to individual preferences), strategies for communicating risk information during a genetic risk assessments have varied greatly, ranging from qualitative approaches (e.g., describing risk for disease as “low,” “moderate,” or “high”) to quantitative (e.g., “34%”). As a result, it is unclear to what extent genetic susceptibility test providers communicate their own uncertainty about the validity of risk estimates. If they did, we would expect uptake of testing would likely to decrease and test recipients to make fewer behavioral changes, in addition to a greater likelihood of negative emotional responses and decisional regret.

The third source of uncertainty addressed here – *complexity* – is relatively unexplored as a reason for pursuing testing, but represents an often-considered, if unaddressed, concern about how genetic susceptibility testing results are communicated. Understandings of genetic susceptibility information are complicated by family histories of disease which may suggest greater or lesser risks for disease, implications of test results for other family members, implications for other conditions (e.g., AD and coronary artery disease in the case of *APOE* testing, breast and ovarian cancer in the case of *BRCA1/2* testing), and the implications of test results for different prevention strategies. These challenges are only exacerbated by the rapid expansion of identified gene-disease associations which have been incorporated into testing that examines multiple genes and conditions simultaneously. Genetic test providers have struggled with balancing the need to be comprehensive about addressing the multiplicity of outcomes

and with the need to present results in a way that enhances the decision-making capability of individuals without exacerbating feelings of unease (Einsiedel, 2006).

Uncertainty stemming from the complexity of the information is likely to be a source of post-disclosure anxiety and may contribute to distress and dissatisfaction with testing. Reducing complexity-related uncertainty following genetic susceptibility testing is likely to require a multi-faceted approach. First is a more judicious selection of the content to be communicated during a genetic risk assessment. Recommendations for genetic counseling of high-penetrance cancer genes involve understanding the questions a person wants answered through testing and tailoring the content of disclosure accordingly (Patenaude, 2005). While the time-intensiveness necessitated by traditional genetic counseling may be impractical on a large scale, a one-size-fits-all strategy to communicating results may do a disservice to individuals by ignoring information that may address individuals' specific hopes for testing and by including information that may be of limited relevance. Thoughtful testing approaches that efficiently communicate information in ways that focus on the specific needs of individual test seekers are likely to minimize the uncertainty associated with the complexity of genetic susceptibility test results.

In addition, test providers will need to format the results of testing in ways that maximize understandings and avoid creating additional uncertainty. Genetic test providers often adopt a "more-is-more" approach to presenting risk information, and try to maximize understanding by presenting results in multiple ways. Evidence suggests that patient understanding of risk information can often be enhanced by presenting results in fewer ways (Zikmund-Fisher, Fagerlin, & Ubel, 2008). The cognitive and emotional

impact of risk information can be changed through slight alterations in the way it is presented, including the addition of interpretive labels (e.g., “abnormal” or “normal”) and the framing of results (e.g., “survival” vs “mortality”) (Zikmund-Fisher, Fagerlin, Keeton, & Ubel, 2007; Zikmund-Fisher et al., 2008). Ideally, the format of risk information would be tailored to match the needs of individual test seekers.

Different forms of uncertainty may affect responses to susceptibility testing results. The inability of susceptibility testing to resolve uncertainty about health, for instance, is likely to have a negative emotional impact upon many who receive genetic risk disclosure (Baum et al., 1997), and such uncertainty has been found to be associated with decisions to have prophylactic mastectomies following disclosure of *BRCA* mutations (Hurley, Miller, Costalas, Gillespie, & Daly, 2001). Similarly, the ability of testing to reduce risk ambiguity can also affect emotional and behavioral responses to information. Distress is frequently experienced by women who receive uninformative *BRCA1/2* results, particularly among those with intolerance for uncertainty (O'Neill et al., 2006).

As with perceived benefits, risks and limitations, it is probable that participants who self-refer to genetic susceptibility testing do so because they have stronger beliefs that testing can reduce uncertainty. The question has not yet been examined empirically, though.

Behavioral Beliefs

Constructs discussed earlier are based on beliefs about genetic susceptibility tests and reasons for seeking testing. This section discusses beliefs about health behaviors.

Perceived Response Efficacy

Health behavior change is often driven by response efficacy perceptions.

Perceived response efficacy is the belief an individual holds that adopting a specific behavior reduces risk for disease (R. W. Rogers, 1975), and has been examined in genetic susceptibility testing research for conditions such as lung cancer (Sanderson et al., 2009) and colorectal cancer (Myers et al., 2007). Some of the greatest concerns about genetic susceptibility tests are that they may result in genetic determinism, compromising individuals' beliefs that behavior plays an important role in disease susceptibility.

Whether or not response efficacy perceptions affect the use of genetic susceptibility tests has been examined in only a few instances. A review of hypothetical testing found that probability of having testing ranged from 10% when efficacious treatments did not exist, 50% when hope for treatment and prevention existed, and 80% when effective treatments existed (Marteau & Croyle, 1998). In the Multiplex Initiative, participants who perceived themselves to have more health habits to change were more likely to follow through on testing (McBride et al., 2009). Interestingly, though, a recent survey of women with a family history of breast cancer found lower interest in hypothetical genetic testing for breast cancer risk in scenarios where behavioral modifiers existed (Graves, Peshkin, Luta, Tuong, & Schwartz, 2011), suggesting that the impact of perceived response efficacy may vary by family history of disease.

Evidence also shows that the process of obtaining a risk assessment has the power to change response efficacy perceptions. A comparison of risk assessments using factors such as blood pressure, serum cholesterol, and weight found no changes in disease susceptibility perceptions, but increases in the perceived response efficacy of exercise

and weight control for preventing heart attacks (Faust, Graves, & Vilnius, 1981). A separate study of health risk appraisals based on lifestyle, family history, and demographic factors implemented in the workplace found that the appraisals increased beliefs that they could take actions to reduce their disease risks (Blue Cross and Blue Shield of Michigan & Health Services Foundation, 1983). What isn't clear, though, are what results from genetic susceptibility information and what results from the overall process of testing. Pre-test education about genetic testing for colorectal cancer risk was found to increase response efficacy perceptions in a pilot study of healthy adults in a primary care setting (Myers et al., 2007). However, genetic risk information itself may decrease response efficacy perceptions. A study of 44 smokers related to a patient diagnosed with lung cancer found slight decreases in perceptions that smoking cessation would decrease lung cancer risk following disclosure of increased genetic susceptibility to lung cancer (Sanderson et al., 2009).

Some evidence exists that suggests that genetic susceptibility testing has a more sophisticated impact on response efficacy perceptions. One proposed mechanism is that genetic testing biases individuals towards biological rather than behavioral or environmental explanations for disease, thereby biasing those who undergo genetic susceptibility testing towards biological rather than behavioral or environmental interventions. A randomized trial of genetic susceptibility testing for familial hypercholesterolemia, for instance, found that individuals disclosed to be at increased risk due to genetic factors believed less strongly in the ability of dietary changes to reduce cholesterol levels but believed more strongly in the ability of medications to reduce cholesterol levels (Marteau et al., 2004). In addition, the expanding nature of

genetic knowledge may make the distinctions between diseases less salient and affect efficacy beliefs. Unpublished interview data from research on genetic susceptibility testing for AD, for instance, suggest that disclosing an additional association between *APOE* and cardiovascular disease causes some individuals to believe the conditions have a shared etiology, thereby making AD seem more preventable. With increasing recognition of the shared genetic etiology of diseases previously considered to be unrelated, it is possible such effects will occur more often in the future.

Whether or not response efficacy perceptions have an association with the way individuals respond to different referral processes is an unaddressed question and may be important to address in the future given the potential for genetic susceptibility testing to have an impact on them.

Self-efficacy

Self-efficacy is the confidence of an individual to successfully perform a specific behavior in a given situation (Bandura, 1977a). Self-efficacy is a powerful predictor of the effectiveness of a health behavior intervention, and plays a central role in popular health behavior theories, including the Theory of Planned Behavior (Ajzen, 1991), social cognitive theory (Bandura, 1977b), and the Transactional Model of Stress and Coping (Lazarus & Folkman, 1984). The increasing popularity of self-regulation in models of genetic susceptibility testing may only heighten sensitivity towards this important psychosocial determinant.

Despite its recognized importance, self-efficacy has received relatively little attention in studies of genetic susceptibility testing. Self-efficacy about understanding test information was found to be an important predictor of attitudes towards testing in

research on Lynch Syndrome testing among a population at increased risk for colon cancer (S. L. Manne et al., 2007) as well as for test uptake in the Multiplex Initiative examining testing of low-impact markers for multiple conditions (McBride et al., 2009). It is likely that other forms of self-efficacy are important determinants of test uptake. For example, self-efficacy with working with information sources has been shown to be important in general health information seeking (Dey, 2004; Merluzzi et al., 2001) and web information seeking (Chiou & Wan, 2007; David, Song, Hayes, & Fredin, 2007; Tsai & Tsai, 2003). Comfort of online genetics communication was an important predictor of its use (Bernhardt, McClain, & Parrott, 2004). The latter behavior is of particular interest considering that direct-to-consumer genetic tests are primarily available via the Internet. Self-efficacy about coping with results is also likely to be an important determinant of genetic test decisions.

Whether genetic susceptibility testing results affect self-efficacy remains an open question, likely because genetic risk information is tacitly assumed to have no association with one's confidence to perform preventive behaviors. What's worth noting is that genetic risk assessments – like non-genetic risk assessments – are often packed into programs that ignore behavioral capability and self-efficacy building strategies that are integral to most programs aimed at modifying health behaviors. Programs like Navigenics' Health Compass provide risk information, but don't connect test recipients to tangible help that may facilitate the transition to healthier lifestyles. There is a common and usually-flawed assumption that risk information by itself is sufficient to motivate behavior change (Becker & Janz, 1987). A more effective way to promote healthier behaviors would be to package genetic risk assessments into more comprehensive health

behavior change programs that would target, among other goals, increasing self-efficacy for preventive behaviors (Strecher & Kreuter, 1995).

Baseline self-efficacy may differ by referral process. A comparison of self-referred and registry-ascertained participants in a diet and exercise intervention for cancer survivors found that self-referred participants had higher levels of exercise and diet control self-efficacy than registry-enrolled participants (Snyder et al., 2008). Given that most susceptibility tests are predicted on providing information rather than skill building and goal achievement, however, such findings may not translate well into current genetic susceptibility testing research.

Illness Perceptions

Cognitive representations of disease are integral to many theories of health behavior and play a central role of the majority of studies on psychosocial research on genetic susceptibility testing. This proposal summarizes the literature on six key constructs from the Health Belief Model (Rosenstock, 1974) and the Common Sense Model of Self Regulation (CSM) (Leventhal, Diefenbach, & Leventhal, 1992): (1) disease susceptibility perceptions, (2) perceived consequences, (3) identity, including disease labels and symptoms, (4) causal beliefs, (5) timeline of disease development, and (6) control over prevention and/or a cure.

Admittedly, how prior research applies to the current generation of susceptibility tests needs to be considered with care. Prior research focused on genes with strong predictive power, such as *BRCA1/2* and HNPCC panels, whereas the current generation focuses on markers with low to moderate predictive power. In addition, prior research focused on single diseases, whereas current genetic susceptibility tests tend to provide

information about multiple conditions simultaneously. Literature from the high-penetrance, single-disease literature is summarized here and should be interpreted with these caveats.

Susceptibility

Numerous studies have shown an association between disease susceptibility perceptions and interest in or use of genetic susceptibility tests. Structural equation modeling of data collected from a cross-sectional survey of residents of upstate New York, for instance, found susceptibility perceptions to be an important predictor of reported likelihood of undergoing a genetic susceptibility test for cancer, mediating the impact of family history, age, and dispositional traits (Bosompra et al., 2000). A parallel study of residents of Vermont, New Hampshire, and Maine found susceptibility perceptions to similarly predict likelihood of undergoing a genetic susceptibility test for colon cancer, also finding it to mediate the impact of family history and dispositional traits (Bunn et al., 2002). Recent data from the Multiplex Initiative did not find susceptibility perceptions to be directly associated with information seeking about the test or test uptake (McBride et al., 2009) although they did have an effect that was mediated by worry, perceptions about consequences, and testing beliefs (Wade et al., 2011). These findings support prior research on hereditary breast and ovarian cancer susceptibility testing (Shiloh & Ilan, 2005; Wang, Gonzalez, Janz, Milliron, & Merajver, 2007). Susceptibility perceptions are important predictors of whether individuals follow through on genetic susceptibility testing, although their impact may be mediated by other psychosocial constructs.

What's more complicated than might be expected is how genetic risk assessments affect susceptibility perceptions. The enthusiasm felt by proponents of genetic susceptibility testing stems from the ability of genetic risk assessment to provide information about the threat of disease and affect risk perceptions, and research on single-condition tests on genes with strong predictive power confirmed that such information does change susceptibility perceptions. However, even in the case of highly penetrant mutations such as those for hereditary breast and ovarian cancer and for Lynch Syndrome, changes to risk perceptions that result from susceptibility testing are often transient (Heshka, Palleschi, Howley, Wilson, & Wells, 2008). Moreover, risk perceptions are often anchored to pre-test levels and resistant to change, whether provided through non-genetic methods (Harle, Padman, & Downs, 2008; Weinstein et al., 2004) or through genetic susceptibility testing or family history analysis (Audrain-McGovern, Hughes, & Patterson, 2003; Linnenbringer, Roberts, Hiraki, Cupples, & Green, 2010). Whether emerging genetic susceptibility tests involving markers with low predictive power will have the ability to change risk perceptions at all remains an open question.

Despite how fundamental the construct is to genetic susceptibility testing, little is currently known about whether disease susceptibility perceptions vary by referral processes.

Perceived consequences

Perceived consequences refer to both the expected health and psychosocial outcomes should illness develop, such as the perceived severity of disease and the potential loss of work. Although some popular theories such as the Health Belief Model

assume stronger severity perceptions would lead to greater test uptake, the opposite was actually observed in the Multiplex Initiative (McBride et al., 2009).

The impact of genetic risk assessments on the perceived severity of diseases has not been directly studied. The consequences of having a “positive” test result may be different in the context of genetic susceptibility testing than for other risk assessment strategies because of the pleiotropic effects of many risk markers (those who seek genetic risk information about one disease may learn about their susceptibility for others) and because of the familial implications of any genetic test result (risk information is provided not only about the test recipient, but also about any blood relations). Similarly to susceptibility testing, little is currently known about whether disease susceptibility perceptions vary by referral processes. Few reasons exist to believe they would, but the question has yet to be addressed with data.

Identity

Identity, per the CSM, refers to the labels an individual affixes to an illness and the symptoms he or she experiences. This definition has little relevance to genetic susceptibility testing given its focus on healthy individuals. However, the strong overlap between how individuals think about genetics with how they conceptualize themselves may help explain its strong appeal to many and affect how people who undergo testing respond to results (Shiloh, 2006).

Affirmation of the self-concept has been argued to be one of the strongest motivators of behavior (Baumeister, 1998). Genetic susceptibility testing, then, may be sought because it provides affirmation to individuals with stronger beliefs about genetic determinism. Moreover, identity representations may provide novel mechanisms for

effecting health behavior change following genetic susceptibility testing. Priming individuals through self-affirmation appears to make them more receptive to persuasive messages (Steele, 1988). If so, we might actually expect health behavior recommendations during a genetic risk assessment to have a stronger effect among those with stronger beliefs about genetic determinism. Such ideas have been proposed in the past (Etchegary & Perrier, 2007; Shiloh, 2006), but have yet to be tested.

In addition, the nature of genetic susceptibility information reframes the threat of illness from one that is individual to one that is kinship-based. Although genetic testing is often articulated as an integral component of “personalized medicine,” genetic susceptibility testing of an individual provides risk information about relatives; and the implications of test results for relatives is often cited as a reason for and against seeking genetic susceptibility testing (Bluman et al., 2003; Edwards et al., 2008; Esplen et al., 2007; Kinney et al., 2001). Familial and group-level behavior change interventions have rarely been applied in the context of genetic susceptibility testing and may represent an underutilized approach to health promotion that is well-suited to genetic susceptibility testing (McBride, Koehly, et al., 2010).

Finally, genetic susceptibility testing may alter or craft new identities. Such processes have already been seen in susceptibility testing involving markers with moderate to high penetrance. For instance, *BRCA1/2* mutation carriers often identify themselves as ‘previvors’ and seek support and information from others with similar identities (Kenen, Shapiro, Hantsoo, Friedman, & Coyne, 2007). While similar established communities created around genetic variants of much lower predictive power have yet to be seen, at least one company marketing genetic susceptibility testing –

23andme – is encouraging the development of a social network predicated on shared genetic information, a strategy that has been found in studies to increase the amount of social support individuals perceive. Such “communities” may provide further opportunities to promote group behavior change.

It is likely that individuals who self-refer to genetic susceptibility testing hold stronger beliefs about the role of genetics to shape identity in addition to holding strong beliefs about the causes of illness. Whether identity beliefs about disease have any association with how people respond to different referral processes is unknown, and identity scales are often omitted in research on genetic susceptibility testing of healthy individuals for multiple conditions (Shiloh, Rashuk-Rosenthal, & Benyamini, 2002).

Causal beliefs

Causal beliefs refer to the cognitive representations individuals hold about how different risk factors, such as genetics, lifestyle, environment and fate, contribute to the development of disease. Much consternation was predicated on fears that genetic susceptibility testing would lead to genetic determinism, causing individuals to believe genetics was destiny and that positive test results would be misconstrued fatalistically as a diagnosis of future disease or negative test results would provide false reassurance that little risk of disease existed. Indeed, studies of related social beliefs such as athleticism, nurturance, and tendency toward violence have found an inverse relationship between genetic causal beliefs and beliefs that such traits are volitional for the individual (Jayaratne et al., 2009). In general, though, such fears have not been borne out empirically. When queried about health specifically, respondents of a population-based survey in the UK believed that genetics plays a strong role in developing disease, but also

recognized the role of behavior and the environment (Sanderson, Waller, Humphries, & Wardle, 2011). Surveys of attitudes towards genetics in the U.S. also found that most people felt that genetics was just one of many factors that determined personality, behavior or health, and that its strength varied according to trait, action or condition (Singer et al., 1998). In fact, exploratory studies suggest that people are resistant to the idea that genetics is the sole determinant of a condition or characteristic (Condit & Bates, 2005; Condit et al., 2001). Findings from research multiplex testing support the assertion: on all eight conditions offered, participants rated the contribution of genetics to on risk for disease as lower than the impact of behavior (McBride et al., 2009).

Causal beliefs may have an impact on health behavior responses to genetic susceptibility testing through effects mediated by other illness representations. Preliminary cross-sectional research on type 2 diabetes, for instance, shows a strong relationship between genetic causal beliefs and perceived personal control for diabetes (Jayaratne, Petty, Gaviglio, Roberts, & Yashar, 2008). A hypothetical study examining mental illness found that psychological causal labels led people to consider the illness less serious and more curable, suggesting that changes in causal beliefs may lead to changes in threat and benefit perceptions. Labeling mental illness as biological in cause did not seem to have any effect in the same study, though (Lam, Salkovskis, & Warwick, 2005).

It is probable that individuals who self-refer to genetic susceptibility testing research hold stronger beliefs about the genetic causes of disease. Some evidence exists to support this assertion: a study of members of a cancer genetics registry found that self-referred members were more likely to report that genetics could increase the risk for

cancer very much (although they tended also rated other causes higher than systematically recruited members) (Henrikson et al., 2007).

Timeline

Timeline refers to how individuals conceptualize the time to develop a disease, its duration, and time for recovery. Although rarely studied in genetic susceptibility testing research, what evidence that does exist suggests that the longer an individual perceives cancer to last, the greater the worry and distress the test recipient reports after testing (van Oostrom et al., 2007b). Also, the closer an individual is to the age of onset of the disease, the more likely adverse reactions may occur. Individuals who perceived themselves to be closer to the age of onset, for instance, reported higher levels of hopelessness following genetic susceptibility testing for Huntington's disease (Codori, Slavney, Young, Miglioretti, & Brandt, 1997). Evidence suggests that timeline cognitions may affect how people respond to genetic susceptibility information.

It is less likely that timeline cognitions affect uptake of testing, or that such cognitions are changed by testing. As discussed earlier, little evidence suggests that age (and by extension, timeline to perceived age of onset) affects uptake of genetic susceptibility tests. High penetrance mutations are often associated with a younger age of onset (NCHPEG, 2007), but it is unclear whether genetic susceptibility testing using markers of weaker predictive power can change timeline perceptions. Few intuitive reasons exist to suggest that timeline beliefs in genetic susceptibility testing research vary by referral processes, but the issue to date has not been examined.

Control

Much attention in the genetic susceptibility testing literature has been devoted to the impact of genetic susceptibility testing on disease control beliefs. Opponents of genetic susceptibility testing argue that testing results may compromise perceived controllability. A qualitative study of parents whose children were genetically tested for familial hypercholesterolemia, a genetic disorder, considered such testing as merely detecting raised cholesterol levels and considered the condition controllable through behavioral modifications. In contrast, parents who considered such testing to be a diagnostic for inherited mutations perceived the condition as uncontrollable and more severe (Senior, Marteau, & Peters, 1999). Preliminary research on type 2 diabetes shows an inverse relationship between genetic causal beliefs and perceived personal control of diabetes (Jayaratne et al., 2008). A meta-analysis that examined the impact of genetic risk assessments in analogue studies and actual testing for obesity, heart disease, depression and diabetes found little evidence of changes to control beliefs, though, at least compared to non-genetic risk assessments (Collins, Wright, & Marteau, 2011). Proponents of genetic susceptibility testing actually argue that it will empower individuals to have a greater control over their health risks. At present, the evidence seems to favor neither side of the argument.

Control has received much attention in the field of genetic counseling. Perceived control is hypothesized to mediate the relationship between actual controllability and emotion and/or problem-focused coping strategies (Shiloh, Berkenstadt, Meiran, Bat-Miriam-Katznelson, & Goldman, 1997). Indeed, genetic counseling appears to increase perceived control which, in turn affects emotion-based coping responses and

psychological responses (J. Keller, 2005; Pieterse, Ausems, Van Dulmen, Beemer, & Bensing, 2005; Shiloh et al., 1997). The association between perceived control and problem-based coping strategies, such as health behaviors, however, appears more tenuous (Shiloh et al., 1997).

What data exists suggest that the impact of genetic susceptibility testing on control beliefs is minimal, but suggests that self-referred participants may be primed for increases. A study of patients attending a genetics clinic with a genetic problem noted substantially greater increases in perceived personal control after genetic counseling among patients who are self-referred compared to referred by other genetic professionals (Berkenstadt, Shiloh, Barkai, Katznelson, & Goldman, 1999).

Perceived behavioral control is often associated with behavioral intentions (Ajzen, 1991). If behavioral control beliefs overlap with disease control perceptions, we might expect self-referred samples in genetic susceptibility testing research to have stronger disease control beliefs.

Emotions

The emotional impact of genetic susceptibility testing has been an important focus of research. Considerable concern has been devoted the possible adverse effects of testing, such as the possibility that test results indicating increased risk for disease will lead to distress, depression and anxiety, or, conversely, no indications of risk might lead to “survivor guilt.” Such fears appear to be exaggerated. Genetic susceptibility testing generally does not lead to long-term distress when provided through clinical genetic counseling services, whether the testing is for a highly-penetrant genetic marker for a condition with few or no preventive options like AD and Huntington’s disease

(Broadstock, Michie, & Marteau, 2000; Green et al., 2009), or a less penetrant markers for conditions with many preventive options like melanoma (Kasparian et al., 2009). Short-term negative emotions are often stronger among carriers of risk-increasing genetic markers than non-carriers (Meiser, 2005), but differences decrease or disappear over time (Douma, Aaronson, Vasen, & Bleiker, 2008; Green et al., 2009; Heshka et al., 2008; Rew, Kaur, McMillan, Mackert, & Bonevac, 2010). In fact, more often, recipients of genetic susceptibility tests show no change or slight improvements in negative emotion after testing compared to before (Heshka et al., 2008; Kasparian et al., 2009; Meiser, 2005; Rew et al., 2010).

Of note, the vast majority of emotional outcomes examined in research on genetic susceptibility testing have ignored positive emotional responses and have instead focused on negative emotions, particularly anxiety, distress, and depression. This omission is surprising given that positive responses, such as relief if found not to be at increased risk, is frequently cited in the context of making decisions about seeking susceptibility testing (Armstrong et al., 2000; Bluman et al., 2003; Edwards et al., 2008). Interviews and self-administered questionnaires of individuals who have undergone susceptibility testing for colon cancer risk or hereditary breast and ovarian cancer risk have found that testing helped them initiate positive changes to their lives (Carlsson & Nilbert, 2007), motivated them to improve relationships, and gave them a greater appreciation for life (Low, Bower, Kwan, & Seldon, 2008). In addition, trends showing a general decrease in negative affect among non-carriers of *BRCA1/2* and HNPCC mutations provide additional support for the likelihood of positive emotional responses (Meiser, 2005).

What evidence that has been collected with respect to positive responses is consistent with the evidence on negative responses. Non-carriers of cystic fibrosis mutations were more likely to report being happy, relieved, or pleased by their results than mutation carriers in a study conducted in the UK three years after testing (Marteau, Dundas, & Axworthy, 1997). Individuals who were tested and found to be non-carriers of *p53* mutations for Li-Fraumeni cancer syndrome, likewise, showed greater levels of post-test happiness than mutation carriers (Dorval et al., 2000). Qualitative analyses of responses to *BRCA1/2* test results found few positive results aside from a sense of relief among 4% of mutation carriers. In contrast, 80% of non-carriers responded in ways that suggested happiness or relief (Lynch et al., 1997).

Emotional responses to genetic information may be affected by the kinds of results individuals expected. Semi-structured interviews with women who received unexpected results after prenatal ultrasounds have found increased levels of anxiety even months after the results (Ahman, Runestam, & Sarkadi, 2010; Sommerseth & Sundby, 2010), and a mismatch between expectations and information may explain qualitative and quantitative findings that individuals who received negative test results during testing for familial adenomatous polyposis (FAP) didn't seem reassured by the information (Michie, McDonald, & Marteau, 1996; Michie et al., 2002). In fact, it is possible to strongly influence affective responses to risk information by simply making test recipients create some sort of risk estimate. In a study that provided risk estimates about breast cancer, 40% of women who estimated their risk beforehand reported relief at the actual figure compared to only 19% of women who did not estimate their risk (Fagerlin, Zikmund-Fisher, & Ubel, 2005). The association between expected and actual test outcomes and

emotional responses to genetic susceptibility testing has not been examined in depth, but preliminary analyses on testing for AD suggest that individuals who are accurate in their expectations of carrying a genetic risk marker have stronger emotional responses than those who are inaccurate (Mork, Uhlmann, Zikmund-Fisher, Yashar, & Roberts, 2009). More research needs to be conducted to tease apart the confounding effects of family history and baseline concern about disease risk.

How test recipients expect to respond emotionally to testing can provide insight into how they actually do respond, too. At times, individuals can predict their emotional responses. A study examining *p53* testing for Li-Fraumeni syndrome and *BRCA1* testing for breast and ovarian cancers showed that individuals who did not have cancer generally reacted as expected (Dorval et al., 2000). Predictions of emotional responses generally fare poorly, though. A subgroup of affected carriers in the same study cited above had greater post-test anger and worry than they expected (Dorval et al., 2000). Sieff et al. examined affective forecasting in the context of HIV testing and found that test seekers both overestimated the general distress they would feel following a positive test result and underestimated the general distress in their lives following a negative test result (Sieff, Dawes, & Loewenstein, 1999). Such findings are consistent with the literature on affective forecasting. Affective forecasting is notoriously inaccurate, especially with respect to medical conditions. Patients with chronic conditions strongly tend to rate their happiness and quality of life much higher than health individuals anticipating the effect of the disorder (Damschroder, Zikmund-Fisher, & Ubel, 2005; Ditto, Hawkins, & Pizarro, 2005; Dolders, Zeegers, Groot, & Ament, 2006; Fried et al., 2006; Riis, Loewenstein, Baron, & Jepson, 2005). In fact, quality of life measures show remarkable

resistance over time, even in the face of lasting physical effects (Bloom et al., 2004; Schroevers, Ranchor, & Sanderman, 2006).

The accuracy of affective forecasting appears to be at least partially associated with how well individuals understand information and explanations. Positive moods following unanticipated events such as spontaneous gifts can be truncated by providing rationales for unanticipated events (Wilson, Centerbar, Kermer, & Gilbert, 2005).

Information-seeking in the context of a threatening health condition has been characterized as a coping mechanism (Luce, 2005), and information itself can have great psychosocial benefit, even in the worst-case scenarios. Individuals have an easier time recovering from negative events when they understand the reasons (Gilbert et al., 1998), and situations that are well-understood fail to generate strong emotions while poorly understood events do (Wilson & Gilbert, 2005). In short, information and information-seeking seems to have a moderating effect on elevated negative or positive affect.

Pre-test psychological functioning may differ between participants who are self-referred compared to those who are systematically recruited. Members who self-referred into a cancer genetics registry reported more symptoms of anxiety and depression than members who enrolled through other means (Henrikson et al., 2007). Such findings must be interpreted with caution, however, as self-referred participants in the same study also endorsed genetics and family history as risk factors for cancer more often, were more interested in genetic testing, wanted more information about cancer, and were more likely to want assistance with cancer prevention and education than population-based participants. Greater levels of anxiety and depression in that study may have been due to differences in cognitions.

Social Support and Social Networks

Social support refers to the kind of assistance provided to an individual through interpersonal relationships. It has been operationalized in many ways, but generally is conceptualized as a function of the instrumental and emotional help available from others (House, Umberson, & Landis, 1998) and may include appraisal and informational dimensions, too (Heaney & Israel, 2008). Given the familial and social group implications of genetic information, social support may play key role in shaping how individuals seek and respond to genetic susceptibility information.

Only a few studies have examined the relationship between social support and uptake of genetic susceptibility testing. A convenience sample of Ashkenazi Jewish women in the Seattle area found social support seeking to be the only variable associated with interest in genetic testing for hereditary breast cancer risk (Bowen, Bourcier, Press, Lewis, & Burke, 2004). More robust associations have been found in the area of how individuals respond to genetic susceptibility testing results. A cross-sectional survey of colorectal cancer patients found greater distress following genetic counseling for HNPCC among those with lower satisfaction with social support (Esplen et al., 2007). Similar results were found in prospective studies among Dutch and American cohorts for following testing for *BRCA1/2* and HNPCC mutations (Gritz et al., 2005; van Oostrom et al., 2007a).

Some commentators have argued that targeting social support represents a promising but underexplored strategy for using genetic susceptibility testing to promote health given how genetic risk is shared among blood relations (McBride, Bowen, et al., 2010). Such communal coping strategies would rely upon the extent to which genetic test

recipients communicate results to family and close others. An important factor that is sure to affect the sharing of results is the size and quality of one's social network.

Social support is a measure of the helpfulness of interpersonal relationships. Social networking is a related concept that assesses the scope of interpersonal relationships. Social networks refer to the number and type of ties an individual has with others, and can be characterized on dimensions such as reciprocity, intensity, and complexity; and by characteristics of the network as a whole in dimensions such as size, homogeneity, and dispersion (Heaney & Israel, 2008; House et al., 1998). Social network analyses have shown that communication about HNPCC testing occurs less among families where mutations have not been identified (Ersig, Hadley, & Koehly, 2011). However, the communication of genetic test results between family members where HNPCC mutations have been identified are more likely to occur between dyads if one member has a mutation or the dyads are spouses or first-degree relatives; or if the relationship between dyads is defined by positive cohesion, leadership, or lack of conflict (Koehly et al., 2003). An understanding of the impact of social networks on the use of genetic susceptibility testing will only become more important with the relentless growth of social media on the Internet and the simultaneous proliferation of companies offering susceptibility tests through the same medium.

Few studies have examined how self-referred participants differ from systematically recruited participants on measures of social support and social networks. An analysis of how participants of a bipolar disorder disease registry learned about it found that patients who self-referred were more likely to be married than participants who learned about the registry through other means (Scholle et al., 2000). However, the

opposite trend with respect to marital status was seen in an analysis of demographic characteristics of individuals who enrolled in a study of AD susceptibility testing (Roberts et al., 2004).

Decision Participation Preferences

While decision participation preferences might be considered a dispositional trait, it is singled out in this proposal because its impact on genetic susceptibility testing uptake and responses is one that is presumed to have a particularly important relationship with referral processes. Using a system proposed by Debra Roter and Judith Hall (Roter & Hall, 1992), decision participation in medical interactions can be characterized as ranging from situations where patients have more control (*autonomy* or *consumerism*) to situations where providers have greater control (*paternalism* or *deferred*). Shared control exists when patients and providers are equally engaged (*mutuality*) or equally unengaged (*default*). The prevailing ideology around genetic susceptibility testing is providing risk information to individuals will empower them and motivate them to adopt healthier behaviors. Important decision theories, such as Self Determination Theory, assert that individuals have an inherent need for autonomy, and that fostering autonomy maximizes intrinsic motivation and the likelihood of sustained behavior change (Ryan & Deci, 2000). Increasing perceived personal control is a stated goal of genetic counseling (Smets, Pieterse, Aalfs, Ausems, & van Dulmen, 2006) and genetic services are often marketed under the auspices of patient empowerment (Bowen, Battuello, & Raats, 2005). In fact, one of the major direct-to-consumer genetic testing companies markets its services by stating, “Our goal is to empower you with genetic insights to help motivate you to improve your health” (Navigenics, 2011).

The assumption that greater decision participation by test recipients universally translates into more effective decision-making or optimal health behaviors may be flawed, however. Indeed, participation preferences are not uniform. A cross-sectional survey of female patients of a primary care practice in Washington State found that while most women preferred autonomous decision-making about genetic testing for breast cancer risk (versus shared decision-making or paternalism), 7% strongly agreed that they would prefer to leave decisions to their providers (Helmes, Bowen, & Bengel, 2002). And while paternalism consistently ranks lowest on decision-making preferences, autonomy does not always appear to be the favored decision-making preference, either. A random-digit dial survey of Americans found that the preferred medical decision-making style to be shared rather than autonomous or paternalism (Murray, Pollack, White, & Lo, 2007). The two studies did not operationalize decision participation preferences the same (Helmes compared the independent rating of each decision style, whereas Murray forced participants to select one type over the other), but it is possible that the differences in findings in these two large population-based studies are due to one study focusing on genetic testing for breast cancer risk specifically while the other addressed medical decision-making more generally.

Decision participation preferences have been found to be related to demographic factors, locus of control beliefs and trust perceptions. Those who have autonomous decision participation preferences tend to be younger and more educated (Helmes et al., 2002), lack a regular doctor and tend to have poorer self-rated health (Murray et al., 2007). In short, they seem to demographically match those who are currently seeking genetic susceptibility testing on many factors. Those who prefer deferring decisions to

providers tend to be older, less educated, have lower incomes, and be of black or Hispanic ethnicity (Benbassat, Pilpel, & Tidhar, 1998; Murray et al., 2007; Roter & Hall, 1992). Those with greater external locus of control beliefs were more favorable towards deferring decisions to their healthcare providers and less favorable towards autonomous decision-making (Hashimoto & Fukuhara, 2004; Helmes et al., 2002). Trust in provider was also an important predictor of decision participation preferences (Helmes et al., 2002). Greater perceived severity of a disease is also to be associated with preferences for deferring decision-making to providers (Benbassat et al., 1998; Roter & Hall, 1992).

In these respects, we might expect processes to have differing effects depending on the context in which it operates. Self-referral to genetic susceptibility testing likely favors those with autonomous decision participation preferences given how control resides with the participant, whereas systematic recruitment might be more favorable to those with paternalistic decision participation preferences. These preferences will likely either match or conflict with the way genetic susceptibility information and subsequent behavioral response options are communicated. How concordance or discordance of decision participation preferences with actual decision processes affects uptake of testing and response to genetic susceptibility testing is addressed in the section that presents the conceptual model.

TEST PROVISION FACTORS

The other side of the genetic susceptibility testing equation is how genetic susceptibility testing is provided and how information is communicated. As mentioned earlier, how genetic susceptibility testing is made available has been a contentious and evolving issue. Currently, outreach strategies mimicking systematic recruitment are

implemented primarily in medical settings and only in cases where a personal or family history of disease suggests a strong genetic component and where proven risk reduction strategies exist. A reluctance to regulate consumer channels has facilitated the emergence of DTC companies that use passive advertising approaches that mimic self-referral. One can imagine approaches such trends changing, however. DTC genetic testing companies may adopt marketing strategies targeted at individuals, and the emergence of low-cost full genome scans raises the potential that all individuals could learn genetic information about themselves if they take the initiative to request it from their care providers. The way individuals respond to information provided during genetic susceptibility testing may not only be affected by referral processes in general, but the way referral processes align with the way information is articulated.

The preceding literature review and the conceptual model proposed later articulate susceptibility testing in a framework that emphasizes intrapersonal determinants of behavior, articulating genetic susceptibility testing as a process that changes certain intrapersonal factors. A comprehensive discussion of important test provider factors that affect uptake of testing and behavioral responses to the information they provide, such as whether and how genetic specialists are reimbursed for services and the training of support staff, is not addressed in this proposal. What follows is a brief discussion of the setting and training of genetic test providers. They are discussed because the setting and training of various genetic susceptibility test providers are hypothesized to be particularly important determinants of whether services are presented in manners that favor different types of referral processes, and are aspects of genetic susceptibility testing that are receiving great attention at present.

Of note, little work has examined how the provision of genetic services interacts with recruitment strategies to affect who enrolls in genetic susceptibility testing research, who follows through with testing, and how people respond to genetic test results. As stated before, susceptibility testing in the clinical setting is available for a limited number of conditions for which the penetrance of risk-increasing variants is high and for which proven risk reduction strategies exist. While the potential exists to compare the profile of patients who self-refer to those tests against those who are referred by a clinician (akin to systematic recruitment) exist, data-driven comparisons are lacking. Marketing by DTC companies to date has been almost entirely using passive strategies favoring self-referral (Mouchewar et al., 2005). Given the lack of existing data, a discussion of how the impact of referral processes may differ according to the setting and training of providers as well as the content and format of pre-test education and genetic risk communication is presented in a more speculative format in the section describing the proposed conceptual model.

Setting

Where genetic susceptibility testing is obtained is a source of great concern to policymakers and commentators. Presently, questions about the analytic and clinical validity of many genetic susceptibility tests, as well as current limitations to the clinical utility of testing, have meant that genetic susceptibility testing is rarely conducted as part of standard clinical practice except for genetic variants of high predictive value when family or personal history was suggestive of a mutation. At the same time, regulation of testing has been relatively limited. The result is that genetic susceptibility testing is most available to the general public in the consumer marketplace.

Despite possible advantages such as ease of access and potentially greater privacy protections, the marketplace may not be the setting of choice for most test recipients. Preliminary results from a survey conducted of undergraduates at the University of Michigan found that about 90% would consider genetic susceptibility testing for depression, heart disease, and AD in clinical settings, but only about 21% would consider testing through websites and 14% would consider testing offered through retail settings (Frysiner, Yashar, Christensen, Roberts, & Uhlmann, 2011). Moreover, obtaining a susceptibility test through the marketplace requires a different set of skills than obtaining it in other settings, such as the clinic. Not surprising given that online communication played an integral in the study, having Internet access was an important determinant of whether individuals logged onto a web site to learn about genetic susceptibility testing in the Multiplex Initiative (although not subsequently associated with the decision to follow through with testing) (McBride et al., 2009). The majority of DTC genetic testing companies are using the World Wide Web as the transactional medium for both purchasing a test and obtaining results (Gollust, Wilfond, & Hull, 2003), meaning DTC settings favor that those who are Internet-savvy with respect to health, namely those who are white, female, younger, educated, and have higher incomes (Pew Internet & American Life Project, 2005).

The consumer setting may not be optimal for facilitating health behavior changes. What work that has been conducted suggests minimal ability of DTC genetic testing to effect health behavior change (Bloss, Schork, & Topol, 2011). Evidence from other risk assessment technologies provides greater insight. A review of the impact of cholesterol, breast and cervical cancer screening programs on health behavior changes found that

healthcare settings to be more effective than workplace or community settings for promoting health behavior changes (Bankhead et al., 2003). Such findings are understandable: changing health behaviors is difficult. The barriers to healthy lifestyles are very often inhibited by limited behavioral capacity, low self-efficacy, and a lack of social support. Where many risk assessment interventions fall short is there is an assumption that changing risk perceptions will by itself motivate health behaviors (Strecher & Kreuter, 1995). Little attention is given to helping individuals develop the skills they need to implement behavior change. While genetic susceptibility testing for common disease is unlikely to be incorporated into standard clinical practice anytime soon, genetic susceptibility testing conducted in clinical settings may result in greater health behavior change than genetic susceptibility testing in other settings because of physicians' experiences in providing resources that facilitate behavior change.

Similarly, workplace settings appear to be more effective than community settings in motivating behavior change following a risk assessment intervention (Bankhead et al., 2003; Giles et al., 2001; Kadison, Pelletier, Mounib, Oppedisano, & Poteat, 1998). Greater control over follow-up, social support, and peer pressure to make health behavior changes have been suggested as explanations for these workplace-community differences (Bankhead et al., 2003). Genetic susceptibility testing in the workplace has generally only received attention due to the potential to lead to employment or health insurance discrimination, although some targeted testing to maximize worker health has been considered (e.g., HLA-DPB1 Glu⁶⁹ testing for susceptibility to chronic beryllium disease) (Holtzman, 1996). What may be more likely to occur is targeted introduction of genetic susceptibility testing among large employers and insurer groups. Navigenics, one of the

major DTC genetic testing companies, for instance, has shifted its focus from recruiting individual customers to targeting large employer groups. Per a Navigenics press release, “the company has successfully integrated into the health and wellness programs of large, self-insured employers by offering large scale preventive genomic programs in order to increase employee motivation to improve lifestyle, enhance participation in existing employee wellness offerings, and improve medical compliance” (Navigenics, 2010).

One additional setting merits mention: the research setting. While most, if not all, studies have provided genetic susceptibility testing in either clinical or consumer settings, only a few studies have provided it outside the purviews of health promotion and only in the name of science. An example of such research is the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) Study of genetic susceptibility testing for AD. Because no proven prevention options exist, study educational materials assert, “there are no proven ways to prevent AD from developing,” and risk information is unaccompanied by specific recommendations for behavior change. Yet, the REVEAL Study is one of the few studies to show data suggesting self-reported changes to behavior such as diet or dietary supplements (Chao et al., 2008; Christensen, Roberts, et al., 2010; Vernarelli et al., 2010). While multiple explanations exist that explain this discrepancy (e.g., perceptions that changing diet and exercise can cause no harm but *might* reduce risk, social desirability on self-reported measures), anecdotal evidence also suggests that study populations enrolled in the study because it was associated with Alzheimer’s research and, therefore, might provide information about prevention strategies not known to the public at large (Christensen, Roberts, Uhlmann, et al., 2011). Participants who are looking for ways to reduce risk for conditions largely considered to be non-modifiable

may self-refer to university settings over others with the hopes that researchers will provide “inside information” that will allow them to make behavioral changes to reduce their risk.

Training

Genetic testing for rare mutations with high penetrance has generally been the purview of medical geneticists and genetic counselors, specialists trained to understand and communicate genetic information. Despite the attention genetic services have received for over a decade, few physicians opt for these career paths, and the field at large is now struggling with the shortage of trained genetic specialists amid the proliferation of genetic services (Guttmacher, Jenkins, & Uhlmann, 2001; Holtzman & Watson, 1998). As of 2010, approximately 1,500 certified clinical geneticists and 2,800 certified genetic counselors practiced in the United States (American Board of Medical Genetics, 2010). Already, genetic services have been strained. With genetics becoming more and more incorporated into medical care, the supply of genetic specialists is unlikely to keep pace with the demand among consumers.

A bevy of recent studies have used a health educator or simply online disclosure, though (Bloss et al., 2011; Gordon et al., 2010; McBride et al., 2008), a strategy that may help alleviate an expected shortfall in genetics professionals. Primary care physicians (PCPs), and physicians of all types, are likely to also help fill the void. In some ways, consumers will benefit. PCPs are generally endorsed as the preferred source of genetic information (Morren, Rijken, Baanders, & Bensing, 2007; Singer et al., 2004), and most consumers consider healthcare providers to be the most credible source of health information (Couper et al., 2010; Marton, 2003). Great concern has been given to the

readiness of medical professionals to respond to advances in genetics (Guttmacher, Porteous, & McInerney, 2007; Khoury, Burke, & Thomson, 2000; McInerney, 2000; SACGHS, 2011), however, and a review of the literature of provider knowledge shows that providers have much room for improvement (Suther & Goodson, 2003). Many physicians are ill-informed about genetic disorders (Greendale & Pyeritz, 2001; Guttmacher et al., 2001; Harris et al., 1999; Harvey et al., 2007; SACGHS, 2004), and patients with such conditions frequently have to educate their care providers about the diseases and manage the course of medical care (Gilmore, 2005). Furthermore, PCPs may have a lower tolerance for the kinds of ambiguous results that are often generated as part of genetic susceptibility testing (Geller, Tambor, Chase, & Holtzman, 1993).

At present, it is unclear how the training of genetic test providers affects the way individuals seek genetic susceptibility testing. Physician recommendations to pursue testing of high-penetrance mutations have been found to be associated with genetic testing decisions (Frazier, Calvin, Mudd, & Cohen, 2006; Peters et al., 2006), but the limited-to-non-existent clinical utility of susceptibility tests of markers with low predictive power makes it unlikely that physicians will recommend the emerging generation of susceptibility tests. It is also unclear how the training of providers affects responses to susceptibility test information. The preponderance of data collected to date (and summarized in this review) were garnered from studies that involved genetic counselors; but the aforementioned data suggests that others will need to fill the void of interpreting genetic information. Primary care physicians have been singled out here and by other commentators (McGuire & Burke, 2008), but other specialists will likely be impacted by emerging genetic services. The National Coalition for Health Professional

Education in Genetics (NCHPEG) has already developed targeted educational programs for dietitians, nutritionists, physician assistants, speech pathologists, dentists and dental hygienists. While it is unlikely that many of these provider types will disclose genetic susceptibility test results in the near term, it is reasonable to assume that they will be called upon to help interpret results in the future.

Pre-test Education and Genetic Risk Communication

The setting of testing and the training of genetic test providers has received the most attention to date from policymakers and academics, but increasing attention is being given to the communication of genetic susceptibility information. Leaders in the field of genetics assert that an essential skill healthcare providers must learn is “communicating genetic information and facilitating informed decision-making by patients” (Guttmacher et al., 2007, p. 153), and trained genetics providers are thought to be able to alter how individuals respond to genetic test information by reframing it in ways that facilitate comprehension, minimize threat appeals (e.g., emphasizing the percent chance that disease will never manifest as opposed to manifest) and maximize coping confidence (e.g., emphasizing the behavioral factors associated with disease risk) (Berkenstadt et al., 1999; Shiloh, 2006). How often comprehension is confirmed (Michie, Lester, Pinto, & Marteau, 2005), genetic counselor directiveness (Weil, 2003), and the way risk information is articulated and framed, and how risk is contextualized (O'Doherty & Suthers, 2007) have all been surmised as affecting how information is understood and retained. Even non-verbal cues are receiving attention (Roter, Ellington, Erby, Larson, & Dudley, 2006).

Thousands of studies have examined health communication interactions and styles. The section that follows focuses on three major aspects of genetic risk information singled out for their relevance to the proposed conceptual model: the content of communications, the mechanisms used to communicate, and the decision processes that are established.

Message Content

What is communicated during pre-test education and disclosure of genetic susceptibility test results will vary from test to test and provider to provider. This section specifically addresses the predictive power, disease information, risk assessment goals, pleiotropic effects, risk presentation, and message framing.

Predictive power. The predictive power of a genetic risk susceptibility test appears to be an important predictor of its use. A recent study that posed various genetic testing scenarios to women with a family history of breast cancer found generally high interest in testing (>50% interest if the cost was free or \$150), with interest increasing as the predictive power of the test increases (Graves et al., 2011), supporting similar qualitative work conducted in Australia in the area of susceptibility testing for melanoma (Kasparian et al., 2007). Given that the reduction of uncertainty is often a motivation for seeking testing, such findings are not surprising.

The predictive power of a genetic risk assessment also appears to be an important predictor of whether test recipients make health behavior changes after a genetic risk assessment. Table 1 provides an overview of some genetic risk assessment studies that have found health behavior responses. For tests such as *BRCA1/2* testing for breast and ovarian cancer risk, where mutations increase risk for disease by at least 5-fold, mutation

Table 1. Overview of behavior changes following genetic susceptibility testing for specific conditions, organized by the predictive power of testing.

| Condition | Gene | Population | Disease risk w marker vs w/o | Behavior | % Changing Behavior |
|---------------------|----------------|----------------------|------------------------------|-----------------------------|--------------------------------|
| Colorectal Cancer | HNPCC panel | Families w. mutation | 69% vs 5% | Colonoscopy ≤ 1 yr | 53-75% vs 0-16% ^a |
| Breast Cancer | <i>BRCA1/2</i> | Families w. mutation | 60% vs 12% | Mammograms ≤ 1 yr | 92% vs 30% ^a |
| Ovarian Cancer | <i>BRCA1/2</i> | Families w. mutation | 40% vs 1% | Screening ≤ 1 yr | 59% vs 8% ^b |
| Alzheimer's Disease | <i>APOE</i> | FDRs of patients | 55% vs 30% | Any preventive behav @ 1 yr | 52% vs 24% vs 30% ^b |
| Lung Cancer | <i>GSTM1</i> | Smokers | 11% vs 8% | Cessation at 2 mo | 35% vs 17% vs 28% ^b |

a Carriers vs non-carriers
b Carriers vs non-carriers vs non-tested

carriers appear between 3 to 8 times more likely than non-carriers to adhere to screening recommendations. For tests such as *GSTM1* testing for lung cancer susceptibility or *APOE* testing for AD susceptibility, where risk-increasing variants increase susceptibility by 1.5 to 2-fold, the differences in behavioral responses are far weaker. Finally, analyses of response to Navigenics' Health Compass panel test (not included in Table 1 because only odds ratios were reported), where results were coded 'orange' if disease risk was 20 percent above average or the absolute risk was greater than 25 percent, showed essentially no differences by risk stratification (Bloss et al., 2011). While such comparisons can be also explained by differences in the behavioral outcomes of interest or the populations enrolled, the likelihood that a genetic test recipient will follow through with testing or make a behavior change following risk disclosure is likely to be strongly correlated with the predictive power of testing.

How predictive power affects decisions about testing and responses to results may be dependent upon numerous factors. For instance, it is likely that testing beliefs about the resolution of uncertainty is contingent to some degree about how such information is presented, as the effect of predictive power is stronger near the ‘poles’ than in the middle (e.g., how individuals respond to changes in risk from 90% to 100% is much stronger than how they respond to changes in risk from 40% to 50% risk); or whether risk is framed negatively or positively (e.g., chance of disease vs chance of remaining disease-free) (Kahneman & Tversky, 1979). What’s almost certain that the mechanisms by which such information changes affect follow through of testing and subsequent post-test responses include both cognitive and emotional mechanisms (Zikmund-Fisher, Fagerlin, & Ubel, 2010); and the predictive power of testing will influence both pathways.

Disease information. It is important to keep in mind that the process of genetic susceptibility testing has the potential to alter illness perceptions in ways that may be unrelated to genetics. Pretest education and genetic risk disclosure often include information related to the physical and social consequences of developing specific conditions and the timeline of potential disease onset, and highlighting the multifactorial etiology of most diseases is an emphasis of most research-related and commercial genetic susceptibility testing programs. Few genetic testing studies have been designed that allow for distinguishing the impact of genetic information independent from the accompanying disease information. It is likely that such information has the potential to affect follow through of testing and subsequent health behavior changes.

Another key point is that what’s communicated during a genetic risk assessment may be only partly what’s known or expected about a genetic marker. Expanding

knowledge about the pleiotropic effects of many genes raises the question of whether and how multi-disease effects of a genetic marker should be communicated. *APOE*, for instance, is a risk factor for both AD and cardiovascular disease (CVD). Preliminary analyses suggest that disclosing the CVD-*APOE* association during a genetic risk assessment for AD may increase the likelihood of health behavior change and reduce distress associated with learning about being a carrier of a risk-increasing allele (Christensen, Roberts, et al., 2010). Whether such findings hold up upon more thorough analysis or in other testing contexts remains to be seen; and the impact of more sophisticated messages (e.g., gene-environment interactions) has been identified as a priority area to be addressed (McBride, Bowen, et al., 2010).

Finally, genetic testing is distinguished from other forms of risk assessment by its implications for family in addition to the test recipient. Although genetic susceptibility testing is often articulated as a part of personalized medicine, its approach relies upon examining inherited factors; and the information it generates not only applies to the test recipient, but also anyone with a shared genetic makeup.

Risk assessment goals and prevention information. There has been general inattention to the overall goal of what's communicated during the testing experience. While great variability exists in how individuals are educated about testing and how results are communicated, they typically emphasize the impact of genetic markers on disease risk while acknowledging that lifestyle also plays a role with a tacit goal of disease prevention through the communication of risk information. What they often do not address is how to make behavior change. Whereas a study like those of smoking cessation following disclosure of *GSTM1* testing for carcinogen metabolism and lung

cancer risk directly addressed smoking cessation and incorporated components such as self-help guides, access to smoking specialists, and nicotine patches (McBride et al., 2002), many – if not most – other genetic susceptibility testing studies did little beyond providing risk estimates and suggesting behavior change.

In fact, the nature of genetic information could enhance the ability of a risk assessment program to lead to health behavior change over other risk assessment approaches by providing insight on how effective different interventions may be. What makes genetic susceptibility testing different than many other risk assessment strategies is its ability to provide information about biological mechanisms of disease. McBride and colleagues have proposed that genetic testing may provide novel avenues to behavior change by elucidating the biological processes to disease and informing intervention choices (McBride, Koehly, et al., 2010). For example, a gene associated with smoking addiction due to its association with nicotine metabolism (*CYP2B6*) may provide insight into whether or not specific smoking cessation drugs may be effective (Lerman, 2006). Similarly, expanding knowledge about gene-environment and gene-behavior interactions may enhance the acceptability of testing and screening programs. While such programs are only now being developed (e.g., Myers et al., 2007), analogue studies suggest that tailoring treatment strategies to genetic predispositions would greatly improve the appeal of health behavior interventions (Wright, Weinman, & Marteau, 2003). Tailored health communications also provide a means of enhancing the appeal of health behavior interventions. As suggested earlier, individuals often hold powerful beliefs about how they are shaped by genetics. Appealing to these genetic identities may provide a way of increasing the persuasiveness of health communications and affect the response efficacy

perceptions of specific health behaviors (Etchegary & Perrier, 2007; Kreuter & Wray, 2003).

Comprehensibility. How information is provided during a genetic risk assessment is a great concern of many opinion leaders. In particular, the complexity of genetic information is made worse by formats that are appropriate for only the well-educated. DTC genetic testing company websites present information written at a college reading level (Lachance et al., 2010). A number of factors may affect not just whether or not information is understood, but how information is interpreted.

One of these factors is the way risk information is presented (*risk presentation*). Genetic test providers have used various formats to communicate the results of genetic susceptibility testing. Options for communicating risk include absolute numerical estimates of lifetime and remaining risk, “synthesized” risk assessments where recipients receive qualitative feedback (e.g., “high”, “average” or “low”), and relative risks comparing the test recipients’ personalized genetic risk against the general or comparable populations. Experts agree that synthesized risk information (e.g., tables, graphs) aids comprehension and facilitates decision-making, but the way different formats affect the cognitive and emotional processing information is an area of ongoing research. Said another way, the same information can have very different effects depending on how it is presented (Fagerlin, Ubel, Smith, & Zikmund-Fisher, 2007).

As with most aspects of risk communication, the impact of risk presentation on how genetic risk information is interpreted is complex. A few generalizations can be made, though. People seem to be able to make greater sense of frequencies compared to percentages (Fagerlin et al., 2007), and their graphical analogues, pictographs, have been

shown to maximize understanding compared to text and tables in a number of studies (Hawley et al., 2008; Tait, Voepel-Lewis, Zikmund-Fisher, & Fagerlin, 2010; Zikmund-Fisher et al., 2008). Adding labels such as “abnormal” or “positive” to results can heighten their ability to raise risk perceptions and increase behavioral intentions (Zikmund-Fisher et al., 2007; Zikmund-Fisher et al., 2010), and framing information against population frequencies can heighten or mitigate its emotional impact (Zikmund-Fisher et al., 2010). These are just a few of the aspects of presentation that alter the psychosocial impact of genetic risk information.

Message *contextualization* is another aspect of risk communication that affects the comprehensibility of pretest education and genetic risk assessment. Most important is whether or not results are articulated in the context of family history for disease. A positive family history is a risk factor for many chronic diseases, reflecting the consequences of genetic susceptibilities, shared environment, and common behaviors. The systematic collection and assessment of family health histories is a potentially valuable tool in preventive medicine, and is crucial in the identification of genetic risk (Acheson, Wiesner, Zyzanski, Goodwin, & Stange, 2000; Khoury, 2003). In some situations, family history information alone can form the basis for offering patients appropriately tailored preventive interventions (Qureshi et al., 2007). In addition, the clinical predictive value of even the most accurate DNA test is strongly influenced by prior probability such as is often conferred by a positive family history. For example, the positive predictive value of the same DNA based test for FAP could rise from about 11 percent—in a patient where no family history information was available—to 99 percent if the patient accurately reported FAP in just one sibling or parent (Rich et al., 2004). Using

genetic susceptibility test results to help explain familial patterns of disease may help test recipients make sense of their information and expedite group-level health behavior interventions (McBride, Bowen, et al., 2010). Tools such as the Surgeon General's My Family Health Portrait Tool may facilitate the collection of family health history information and has recognized utility among healthcare providers (Owens, Marvin, Gelehrter, Ruffin, & Uhlmann, 2011). However, despite its utility in preventive medicine, the collection and use of family history information has been an ongoing challenge, however (Valdez, Yoon, Qureshi, Green, & Khoury, 2011).

Directiveness. A last aspect of pretest education and genetic risk assessment reviewed here is the directiveness of communications about whether or not to follow through with testing and whether or not to make health behavior changes. The dominant paradigm for discussing susceptibility testing and communicating genetic susceptibility information emphasizes individual choice and responsibility. Because the majority of genetic susceptibility tests provide risk information with limited to no clinical utility, however, test providers often have little reason to recommend either following through with testing or adopting health behavior changes beyond those that would be made regardless of genetic susceptibility testing results. Moreover, when testing is available in clinics, those who offer testing – genetic counselors – generally operate under an ethos of non-directiveness, meaning that they do not try to influence decisions of patients (although directive approaches are gaining more attention (Hodgson & Spriggs, 2005)). The responsibility for initiating health behavior change lies with test recipients, with only a few exceptions. This lack of directiveness is consistent with referral processes that encourage proactive action on the part of research participants, namely self-referral. In a

similar way, we might expect studies with more directive recommendations for uptake of testing and health behavior change to show stronger effect sizes in studies where participants are responding to communications from researchers, namely systematic recruitment. The Family Healthware Impact Trial is an example of one large study which issued specific behavior change recommendations based on family history and behavioral risk factors to a population that was systematically recruited from primary care settings. Consistent with the hypothesis presented here, results suggest small but statistically significant increases in fruit and vegetable intake and physical activity (Ruffin et al., 2011).

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CHAPTER 3

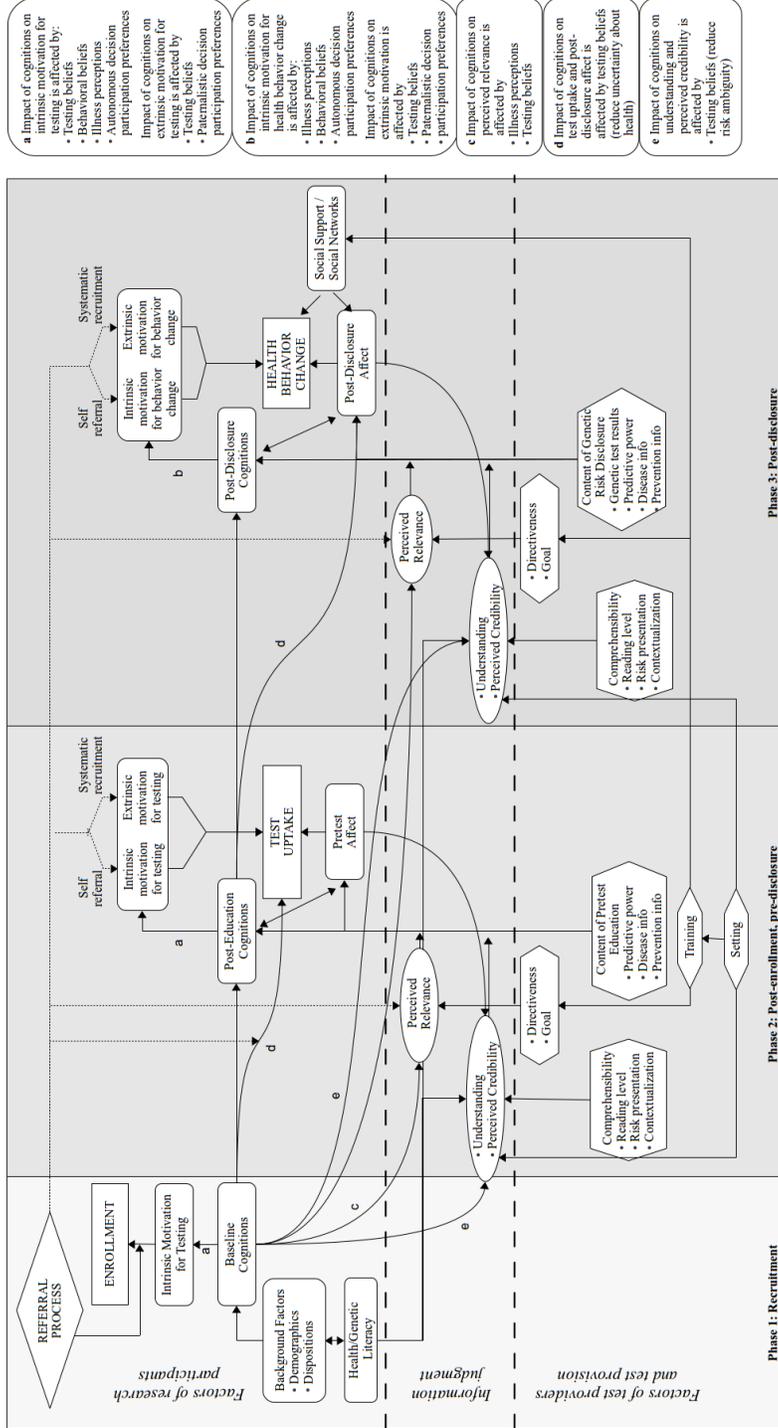
PROPOSED CONCEPTUAL MODEL

Figure 2 presents the original conceptual model which served as the basis for the analyses presented in this dissertation. Although I tested only portions of it in the work summarized in Chapters 4-6, I describe it in full here for consideration in future work.

The model conceptualizes the genetic susceptibility testing as a multi-phase process, with three sequential behavioral outcomes: (1) a recruitment phase ending with enrollment, (2) a pre-disclosure phase ending with uptake of testing, and (3) a post-disclosure phase ending with health behavior responses to genetic risk information. These phases are distinguished in the model through the use of different background shades; and behavioral outcomes of interest are emphasized with capital letters. The model also distinguishes between factors of the genetic test recipient (represented with rectangles), factors of genetic test provision (represented with hexagons); and judgments based on the interactions between the two (represented with ovals).

Per the model, enrollment in genetic susceptibility testing research is a function of baseline motivation. Furthermore, the model posits that both uptake of testing and post-testing changes to health behaviors are determined by motivation and affective states. Motivation itself is conceptualized as a function of cognitions, social factors, and referral

Figure 2. Conceptual model describing the impact of referral processes on enrollment in genetic susceptibility testing research, test uptake, and subsequent changes to health behaviors.



a Impact of cognitions on intrinsic motivation for testing is affected by:

- Behavioral beliefs
- Illness perceptions
- Autonomous decision participation preferences

Impact of cognitions on extrinsic motivation for testing is affected by:

- Testing beliefs
- Paternalistic decision participation preferences

b Impact of cognitions on intrinsic motivation for behavior change is affected by:

- Illness perceptions
- Behavioral beliefs
- Autonomous decision participation preferences

Impact of cognitions on extrinsic motivation is affected by:

- Testing beliefs
- Paternalistic decision participation preferences

c Impact of cognitions on perceived relevance is affected by:

- Illness perceptions
- Testing beliefs

d Impact of cognitions on test uptake and post-disclosure affect is affected by testing beliefs (reduce uncertainty about health)

e Impact of cognitions on understanding and perceived credibility is affected by:

- Testing beliefs (reduce risk ambiguity)

processes; and cognitions and affect are altered by information communicated by genetic test providers during pre-test education and/or genetic risk disclosure through pathways moderated by the judged relevance and credibility of the information, as well as how well it is understood. These moderators are affected by the goals of the test provider and the comprehensibility and directiveness of communications which, themselves, are affected by the setting of the test and the training of test providers.

Referral processes, represented by a diamond at the top of this model, influence behavioral outcomes in three ways depicted with dashed lines. First, they affect the type of participant who enrolls in genetic susceptibility testing research. The barriers individuals must overcome to enroll in genetic susceptibility testing research are presumably higher when self-referral processes are used, compared to systematic recruitment. In the former case, participants must both identify an opportunity and then be proactive about contacting study staff whereas in the latter case, participants simply respond to an opportunity presented to them. It is probable that self-referral strategies enroll populations with greater intrinsic motivation for testing and cognitions more favorable towards testing than systematic recruitment strategies. The second mechanism the proposed model suggests, applicable to both uptake of testing and health behavior changes, is that referral processes affect the locus of motivation; and that the act of self-referral primes participants to be intrinsically motivated whereas the response to systematic recruitment primes participants to be extrinsically motivated. A third mechanism, also applicable to both uptake of testing and health behavior changes, suggests that referral processes affect the perceived relevance of information provided during pre-test education and genetic risk disclosure and, thereby, affect the cognitive and

emotional impact of the information and subsequent decision-making and behavior change.

The overall model and its theoretical bases are explained in more detail in the section that follows. A justification for focusing on different loci of motivation based on Self Determination Theory is presented next, followed by a discussion of cognitive and affective pathways to decision-making and behavior change based on the Common Sense Model of Self Regulation. The influence of information provided during pre-test education and genetic risk assessment, predicated on the Elaboration Likelihood Model, comes after that, along with a discussion about the impact of uncertainty. Finally, the section touches on the special role social support and social networks may play in responses to genetic susceptibility information.

DISTINGUISHING INTRINSIC AND EXTRINSIC MOTIVATION

A key aspect of the conceptual model serving as the basis for this dissertation is a differentiation between intrinsic and extrinsic loci of motivation. Motivation is tacitly a central determinant of behavior in many, if not most, individual-level theories of health behavior. What is often ignored, however, is delineation of whether the motivation stems from internal or external sources and how different psychosocial constructs contribute to each form in different ways.

An extensive body of literature from psychology and education has focused on the differential impact of intrinsic and extrinsic motivation. Herzberg compared the impact of extrinsic motivators, such as salary, benefits, and policies in the workplace against intrinsic motivators, such as challenging work and responsibility, finding the former to be associated with job dissatisfaction and the latter to be associated with positive job

satisfaction (Herzberg, 1973). Educational research has shown a consistent positive relationship between intrinsic motivation and educational achievement (Cordova & Lepper, 1996; Gottfried, 1985; Lepper, Corpus, & Iyengar, 2005), and some work has found negative associations between extrinsic motivation and performance in the classroom (Lepper et al., 2005). In the area of health, studies have generally found better treatment adherence and lasting health behavior changes following interventions that favor intrinsic rather than extrinsic motivation (Ryan, Patrick, Deci, & Williams, 2008).

Such findings are consistent with Self Determination Theory (SDT). SDT generally asserts that intrinsic motivation is more likely to result in positive and lasting behavior change (Ryan & Deci, 2000). In addition, SDT posits that intrinsic motivation is maximized in situations where autonomy is encouraged, when individuals feel competent, and when individuals feel a sense of relatedness to others they are close to or working with. Restated using the concepts found in the model, intrinsic motivation is maximized in contexts (like self-referral) that favor autonomy, when self-efficacy about testing is high, and when social support is strong and information provided is relevant. SDT would suggest that the likelihood which individuals follow through with testing and the way they respond behaviorally to genetic susceptibility information may be a function not only of overall motivation, but also the strength of intrinsic and extrinsic motivation separately. Moreover, SDT suggests that the act of self-referral – a process that maximizes autonomy – causes individuals to have greater intrinsic motivation about following through with testing or making behavior changes following genetic risk disclosure whereas systematic recruitment causes individuals to have greater extrinsic motivation for the same outcomes.

The proposed model recognizes the distinct and differential impact of intrinsic and extrinsic loci of motivation. More importantly, it suggests that each form of motivation arises from a different set of determinants. With respect to motivation for testing, the preceding literature and model suggest that intrinsic motivation is nurtured not only by referral processes that favor self-referral, but may also be a function of positive beliefs about the benefits of testing or the ability of testing to satisfy curiosity and stronger beliefs that behavior changes can reduce risk of disease. Illness perceptions such as stronger disease susceptibility perceptions, weaker severity perceptions, and identity and causal beliefs that favoring heredity and genetics may also be related to greater intrinsic motivation. Furthermore, intrinsic motivation is assumed to be stronger among those with decision participation preferences that favor autonomy. Extrinsic motivation for testing, in contrast, is maximized in situations where systematic enrollment processes are utilized. Extrinsic motivation may also be determined by the strength beliefs about the benefits of testing or the ability of testing to satisfy curiosity, but not by other cognitions. In addition, extrinsic motivation is assumed to be stronger among those with decision participation preferences that favor paternalism.

Health behavior changes following testing are also assumed to be a function of both the intrinsic and extrinsic motivation test recipients have to change behaviors. In fact, the model posits that intrinsic motivation for health behavior change is maximized in situations where self-referral occurs; but is also determined by behavioral beliefs and illness perceptions. Extrinsic motivation for health behavior change, in contrast, is considered to be maximized in instances of systematic recruitment. The cognitions that are important for predicting post-disclosure behavior change, however, are assumed to be

different than those that determine test uptake: extrinsic motivation is thought to be a function of testing beliefs related to their ability to empower test providers, but is assumed to be determined by similar behavioral beliefs and illness perceptions as affecting intrinsic motivation.

Intrinsic and extrinsic motivation for testing and health behavior changes are also assumed to be affected by information provided during pre-test education and genetic risk assessment, respectively, through pathways mediated by changes in cognitions. These pathways are discussed in the section that addresses those parts of the testing process in greater detail. First, this proposal addresses factors that determine or work in tandem with motivation as primary determinants of the outcomes of interest.

COGNITIVE AND AFFECTIVE PATHWAYS

While motivation is central to the proposed model, its influence on outcomes of interest is assumed to operate in tandem with other determinants, particularly affect. Affect is often ignored in models of decision-making and health behavior. This omission occurs despite consistent evidence that decisions and behaviors frequently contradict predictions from rational models (Loewenstein, Weber, Hsee, & Welch, 2001; Mellers, Schwartz, & Ritov, 1999; Slovic, Finucane, Peters, & MacGregor, 2004), and emotions such as anxiety are often associated with preventive measures following genetic susceptibility testing, independent of the impact of results on disease beliefs (Schwartz et al., 2003). The importance of affect is further supported by a growing body of neurobiological and neuroimaging evidence that shows that emotions affect decisions through processes that are distinct from cognitive reasoning (Arnsten, 1998; Bechara, Damasio, Tranel, & Damasio, 1997). Emotions appear to play an important role in

determining how people seek and respond to genetic susceptibility testing, and one that is distinct from cognitions.

Many theories have recognized these dual processes. The backbone of the conceptual model presented here is based on the Common Sense Model of Self Regulation (CSM). CSM posits that behaviors, such as follow through of testing and health behavior changes, occur as coping responses to stressors such as the uncertainty of future illness or indications of increased risk of disease through mechanisms that include both cognitive and emotional pathways (Leventhal, 1970; Leventhal, Diefenbach, & Leventhal, 1992). CSM provides a suitable framework for understanding how pre-test information, as well as genetic risk information itself, can affect uptake of testing and health behavior changes.

CSM holds that the way individuals self-regulate and respond to stressors requires coherence with cognitions about illness (in addition to coherence with culture and personality). For example, an individual who perceived diabetes as uncontrollable would not change his diet to prevent its onset; and an individual who perceived heart disease as caused by a lack of exercise would increase his physical activity if he wanted to reduce his risk. Furthermore, CSM recognizes that emotional responses to stressors alter behavioral decisions both directly and indirectly. While it is well-recognized that cognitions have an impact on affective states, the reciprocal relationship is often ignored. Fear among individuals with low response efficacy perceptions or low self-efficacy for preventive behaviors can raise susceptibility perceptions, though (Witte, 1992), and individuals who perceive “affect rich” consequences to treatment, such as wound infections, will often opt for treatments with higher chance of death but fewer potential

complications (Amsterlaw, Zikmund-Fisher, Fagerlin, & Ubel, 2006). Strong negative emotions can decrease information comprehension and self-efficacy (Bandura, 1977). Moreover, the kinds of emotions an individual feels can affect what cognitive factors are important in decision making. For instance, at low cancer worry levels, individuals' interest in genetic testing depended on the perceived benefits of testing, whereas at high worry levels, interest was high regardless of perceived benefits (Cameron & Reeve, 2006). These are just a few examples of the associations between affective states and cognitions about disease, behavior, and testing.

CSM has been used by other researchers to model genetic susceptibility testing. Gooding and colleagues suggested CSM as one basis for better understanding how genetic susceptibility testing can be motivated by the desire to reduce uncertainty and gain a sense of control (Gooding, Organista, Burack, & Biesecker, 2006). Shiloh used CSM as a foundation for conceptualizing the process of genetic counseling and its impact on decision-making as it related to undergoing testing and making protective behavior (Shiloh, 2006). These models expand traditional models of responses to genetic susceptibility information by recognizing the importance of emotional determinants and response to information.

Regarding cognitive pathways, the model presented here asserts that information – the predictive power and capabilities of testing, disease information, and the ability of preventive behaviors to reduce disease risk – provided during pretest education causes changes to testing beliefs, behavioral beliefs, and illness perceptions, thereby affecting motivation for testing. Pre-test information also provokes emotional responses, such as worry, distress, or relief. The likelihood of following through with testing is altered by

these changes in cognitions and emotions. Similarly, risk estimates, disease information, and prevention information provided during genetic risk disclosure has effects on illness perceptions and behavioral beliefs, as well as emotions. Behavioral responses ensue as part of the process of coping with such changes.

It should be noted that the cognitive pathways as presented in this proposed model are more inclusive than those typically proscribed by CSM. In an unaltered form, CSM may be insufficient for modeling how people respond to the current generation of genetic susceptibility tests because of its emphasis on illness perceptions and its inattention to behavioral or testing beliefs. While CSM has support in the area of predictive testing using markers with strong predictive value for single diseases (see Shiloh, 2006), it may not be as applicable to current susceptibility tests using markers of lower predictive value for multiple conditions. Information provided during pre-test education or genetic risk assessment about the current generation of genetic susceptibility tests may lack the ability to alter illness perceptions. Moreover, CSM's focus on negative emotional responses fails to recognize the emergence of susceptibility testing as "gentertainment." For these reasons, the model proposed here incorporates an expanded consideration of cognitions as well as considering positive emotional responses in addition to negative ones.

An Expanded Consideration of Cognitions

The model recognizes the role of beliefs specific to preventive health behaviors in test uptake and health behavior changes following testing. Response efficacy and self-efficacy are key components of numerous health education theories and often predict how quickly a new technology is adopted (Rogers, 2003). Self-efficacy is also a core predictor of intrinsic motivation per Self Determination Theory (Ryan & Deci, 2000). In fact, self-

efficacy about understanding genetics is one of the few factors found to be predictive of test uptake in studies of genetic susceptibility testing using markers with low predictive power, and stronger predictors of test uptake than illness perceptions (McBride et al., 2009). Per the model presented here, greater self-efficacy towards testing, as well as stronger response efficacy beliefs about preventive behaviors, increase intrinsic motivation for testing. In addition, the model states that stronger response efficacy and self-efficacy beliefs about preventive behaviors are associated with greater uptake of preventive behaviors through pathways mediated by intrinsic motivation. Although behavioral beliefs are generally omitted from conceptual models predicting testing or behavior change based on CSM, they are central in other stress and coping theories (e.g. the Transactional Model of Stress and Coping (Lazarus & Folkman, 1984)) and are likely to be affected by pre-test education and genetic risk assessment.

The model also incorporates testing beliefs into its consideration of cognitions that change in response to information provided during the testing process. Beliefs about the benefits, risks and limitations of testing are consistently strong predictors of whether or not individuals follow through with genetic susceptibility testing, whether testing addresses single conditions or multiple ones; and the model assumes that positive beliefs about testing are associated with higher levels of both intrinsic and extrinsic motivation to follow through with testing. The model does not assume an effect of testing beliefs on intrinsic motivation for health behavior change given that beliefs about what testing can achieve intuitively has little direct relationship with how people respond to risk information. However, it is likely that testing beliefs may affect extrinsic motivation to the extent that individuals perceive testing as having the ability to empower physicians

and test providers. Furthermore, testing beliefs may have an indirect effect on intrinsic motivation by affecting the perceived relevance of information, a relationship addressed in the subsection about pretest education and genetic risk disclosure.

Moving Beyond Negative Affect

The second major deviation from CSM posited here is an acknowledgment that positive emotional states may be just as important determinants of behavioral responses as negative emotional responses. As detailed in the literature review, psychological relief is often a motivation for seeking genetic susceptibility testing, and the marketing of tests with low predictive power to healthy individuals may be as much a desire for curiosity as any desire to be seeking health benefits. Increasing attention in health behavior and psychology acknowledges differences in behavioral responses depending on whether events are framed as gains rather than losses or rewards rather than punishments (Berridge & Robinson, 2003; Kahneman & Tversky, 1979; Zikmund-Fisher, Fagerlin, Keeton, & Ubel, 2007). Models of genetic susceptibility testing need to acknowledge the potential for positive emotional affective responses, not just negative ones.

Examining positive responses may yield different results than research focused on negative emotions. Loss aversion is a well-recognized psychological response that shows that individuals react more strongly when outcomes are framed as loss rather than gain (Kahneman & Tversky, 1979), and a recent survey examining attitudes towards genetic testing for low-penetrance markers of breast cancer risk found greater interest when testing was framed as detecting a 25% increase in risk rather than a 25% decrease in risk (Graves, Peshkin, Luta, Tuong, & Schwartz, 2011). Such findings are support a growing

body of evidence from the biopsychology literature that reward and loss activate distinct neural pathways (Vartanian & Mandel, 2011).

Based on what is known about the impact of negative emotions, it is likely that positive emotions will be associated with a greater likelihood of test uptake, whereas the association of emotions with health behavior changes will be more sophisticated, with greater levels of health behavior change generally occurring at higher levels of negative affect and lower levels of positive affect (fear, in conjunction with strong response efficacy beliefs, often leads to preventive behavior change). These relationships are primarily speculative, however, and will need to be tested empirically.

PRE-TEST EDUCATION AND GENETIC RISK COMMUNICATION

Great variability exists in the ability of education and information to alter cognitions and affective states. Per the conceptual model presented here, the degree to which test results, the predictive power of the test, disease information, and prevention information alter cognitions and affective states is determined by the way information is judged as a function of its *perceived relevance*, how well individuals *understand* it, and its *perceived credibility*. Such assertions are based primarily upon the Elaboration Likelihood Model, a communication theory that asserts that messages are processed in one of two manners: central processing, and peripheral processing (Petty & Cacioppo, 1983). In the case where relevance is high and a person has the ability to understand the information, central processing occurs and argument strength determines the persuasiveness of the information. If relevance is low or the person is unable to understand the message, peripheral process occurs and heuristics – *credibility*, in particular – determines the persuasiveness of the communication.

Genetic information may have greater perceived relevance and credibility than other types of risk information due to power popularly attributed to genetics by the public and through the media; and how individuals understand genetic information is complicated by limited health and genetic literacy as well as by the complexity by which genetic information is commonly communicated. These judgments are discussed in more detail in the subsections that follow, especially with respect to the potential impact of referral processes on them.

Perceived Relevance

Among the most important determinants of how information affects cognitions and emotions is its perceived relevance (Petty & Cacioppo, 1984). Personal relevance has been defined as the personal meaning of information to an individual, encompassing dimensions such as the number and magnitude of its consequences and the match of the information to an existing need (Petty & Cacioppo, 1986). Evidence to support that relevance affects the way information is processed has been bolstered in recent years with results from brain imaging technologies, such as functional magnetic resonance imaging, showing a greater degree of neural activity in response to personally tailored health information (Chua, Liberzon, Welsh, & Strecher, 2009; Falk, Berkman, Whalen, & Lieberman, 2011). Perceived relevance is gaining attention in discourses of genetic information behavior (Etchegary & Perrier, 2007) and has been proposed as an integral determinant of genetic information seeking due to the assumption that genetic information is perceived as more personal than other types of risk information (Johnson, Andrews, & Allard, 2001).

Referral processes may influence the perceived relevance of genetic susceptibility testing information through their alignment – or lack of alignment – with the directiveness of recommendations for testing or behavior change. Evidence to support the importance of how referral processes align with the directiveness of testing recommendations may be drawn from the literature on decisional satisfaction. Satisfaction with decisions is maximized when decision processes match decision participation preferences. A survey of women recently diagnosed and surgically treated for breast cancer, for instance, found greatest decisional satisfaction and lowest decisional regret not among those with the most patient involvement in decision-making, but among those where decision participation preferences matched the encounter (Lantz et al., 2005). Decision participation preferences similarly moderated the relationship between the decision process and satisfaction among Taiwanese patients with Type 2 diabetes (Lee & Lin, 2010). Further support for this argument may be drawn from the literature on genetic counseling, particularly in work involving groups with distinctive views of physicians and healthcare professionals. The non-directive approach to genetic counseling is often criticized as being poorly suited for communities such as Latinos that tend to view physicians as experts who are better suited to make decisions than patients (Penchaszadeh, 2001). Moreover, interviews and observation of pregnant Latinos considering amniocentesis suggest that the reticence of genetic counselors to engage in a directive manner can leave patients feeling as if the counselor is not listening to them, thus leading to greater rates of test refusal (Browner, Mabel Preloran, Casado, Bass, & Walker, 2003). Similarly, interpreters who translated clinician advice with an authoritative, judgmental tone engendered more trust and rapport with Latinos

considering amniocentesis than translators who adopted a distant, nonjudgmental tone (Preloran, Browner, & Lieber, 2005).

Admittedly, shared decision-making is not the same as the directiveness of health communication; and decisional satisfaction is a questionable representative for uptake of testing or health behavior changes. What those studies do show, however, is that the impact of health communications may be greatest when their directiveness is aligned with preferences and expectations about decision making preferences. Of note, decision participation preferences are identified in the literature review of this proposal as a separate dispositional trait that may play an important role in determining who enrolls in genetic susceptibility testing research according to what referral processes are used. To the extent that referral processes *establish* a narrative that favors certain decision-making preferences, though, they will have an impact above and beyond those held prior to a subject's enrollment in research.

The model proposed here also acknowledges additional factors that may influence the perceived relevance of genetic susceptibility testing information independent of referral processes or decision participation preferences. A criticism of many personalized risk assessment interventions, whether based on genetic information or whether based on other factors such as cholesterol or blood pressure levels, is that they provide information presuming that risk information alone will be powerful enough to motivate health behavior change (Strecher & Kreuter, 1995). They thus ignore information that may be of most relevance to test recipients, namely ways to *reduce* disease risk or overcome barriers to health behavior as low behavioral capacity or low self-efficacy. Relevance is generally maximized when testing beliefs align with the content of pre-test education and

counseling (Rusbult & Van Lange, 1996). The extent to which pre-test educational materials present information that aligns with the test beliefs of participants will impact the perceived relevance of the information provided. More specifically, relevance may be greatest when disease prevention is the most important testing belief, and when the goal of the genetic risk assessment is prevention. Illness perceptions are also likely to affect how relevance of pre-test information is judged. Perceiving susceptibility to disease to be high, the consequences of disease to be severe (if anxiety is low) or the timeline to develop disease may increase the salience and perceived relevance of educational materials. In addition, information that emphasizes the behavioral determinants of disease may conflict with identity and causal beliefs that favor genetics.

In sum, perceived relevance is assumed to be maximized when participants are self-referred, decision participation preferences are autonomous, and communications are non-directive; or when participants are systematically recruited, decision participation preferences are to defer, and communications are directive. The aforementioned data also show that the directiveness of pre-test education or genetic risk disclosure varies by the training of the genetic test provider, with genetic counselors being less directive than other types of providers. Furthermore, the perceived relevance of pre-test education and genetic risk disclosure is assumed to be affected by the match of testing beliefs with the goals of the risk assessment, and illness perceptions.

Understanding

Ability to understand information is contingent upon many factors, including knowledge (Wood, Kallgren, & Preisler, 1985), message comprehensibility (Petty & Cacioppo, 1986) and affect (Arnsten, 1998). Such factors are particularly notable in the

context of genetic susceptibility testing given current levels of health and genetic literacy among the public, the way information about genetic susceptibility testing is currently communicated, and the psychological impact of genetic susceptibility information.

As noted in the literature review, health and genetic literacy levels among the public are low by any measure. Such findings are concerning given that genetic susceptibility information is not only extremely complicated, but test providers tend to present such information in a format befitting only the most educated individuals. A review of DTC genetic testing company websites, for instance, found that the average site presented information written at a grade 15 reading level (Lachance, Erby, Ford, Allen, & Kaphingst, 2010). Moreover, the amount of information genetic tests can generate, particularly when multiplex panels are used, is immense and may further compromise the ability of individuals to understand it. Addressing too many issues simultaneously or increasing the amount of information provided during risk communication appears to compromise recall and comprehension (Zikmund-Fisher, Angott, & Ubel, 2011; Zikmund-Fisher, Fagerlin, & Ubel, 2008, 2010).

The combined effect of poor health/genetic literacy and low comprehensibility may compromise the ability of individuals to make sense of what's shared during genetic susceptibility testing. Such confusion can be compounded by negative emotional reactions, which often cause individuals to blunt out information or attend to information selectively (Petty & Cacioppo, 1986; Power & Dalgleish, 1997). When understandings are poor, individuals are biased to process pre-test education and genetic risk disclosure peripherally, making the persuasive power of communications more contingent upon the

credibility lent to genetics more generally than to the quality of evidence presented during education or risk disclosure, specifically.

In sum, understanding is posited in the model to be higher when pre-test education or genetic risk communication are comprehensible as a function of having a low reading level and addressing fewer topics; as well as when the health and genetic literacy level of participants is high and when negative emotions – distress and anxiety, for example – are minimal. Referral processes are not hypothesized to have direct effects upon understanding of information, but may influence understandings by influencing the population of participants who enroll in genetic susceptibility testing research and through more complicated pathways that affect emotional responses to information.

Perceived credibility

In the event that a message is judged to be irrelevant or a person is to process the information, peripheral processing occurs and persuasion is generally a function of heuristics (Petty & Cacioppo, 1983). An important heuristic that may be particularly important in the area of genetic susceptibility testing is perceived credibility.

Credibility is the judgment of the accuracy of information, and may or may not correspond to objective accuracy (Rieh & Danielson, 2007). It is contingent on many factors, including the perceived trustworthiness and expertise of the information source (Fogg et al., 2001; Wilson, 1983). The issue of credibility is particularly important in the area of genetic susceptibility testing because genetic information seems to be more credible than other types of risk information. The public often assigns power to genetics that does not exist. A recent survey of Western Australians, for instance, found that over 10% believed that cancer and heart disease was entirely genetic and that environment did

not play a role (Molster, Charles, Samanek, & O'Leary, 2009). The effect of such beliefs is that individuals tend to overestimate the abilities of genetic tests. A nationally representative Internet survey of Americans, for example, found that more respondents believed that testing for traits such as intelligence and strength existed (26%) than believed that it did not exist (22%) (Genetics and Public Policy Center, 2004). In a randomized trial of genetic susceptibility testing for AD, participants who received genetic risk assessments based on *APOE* genotype, gender, and family history were more likely to align their susceptibility perceptions to disclosed estimates than participants receiving identical estimates that did not incorporate *APOE* testing (LaRusse et al., 2005).

Perceived credibility may be critical to monitor given the lack of regulation, particularly in the consumer marketplace. The Clinical Laboratory Improvement Amendments (CLIA) ensure the quality of the testing process but ignore whether the tests have any reasonable ability to predict disease (Hogarth, Javitt, & Melzer, 2008). Many tests currently available in the consumer marketplace arguably have limited actual credibility, being validated on a small set of genome-wide association studies (Hogarth et al., 2008; Janssens et al., 2008). Moreover, initial forays into full genome sequencing to predict disease risk have shown that the basis for assessing SNP importance – public databases like dbSNP and the Human Gene Mutation Database – are oftentimes contaminated by associations claiming to be clinically important but actually much less predictive (Ross, Hambuch, O'Daniel, Murray, & Bentley, 2011). Yet, consistently among the least important perceived barriers was that tests might provide inaccurate information (Jacobsen, Valdimarsdottir, Brown, & Offit, 1997). Certainly, credibility

works in both directions, and test recipients who receive ‘beneficial’ results often don’t believe it. Semi-structured interviews with individuals who received negative results during FAP genetic testing, for instance, found that a subset of test recipients adhered to increased bowel screenings because they did not trust the results (Michie et al., 2002). Nevertheless, the greater tendency is that the public believes genetic susceptibility tests are more capable of achieving and what information they can actually provide.

Credibility is posited in this proposal to be a function of a person’s health and/or genetic literacy, particularly conceptual knowledge related to how genetic risk factors influence the risk for multifactorial disease. Consumer genetic test providers have been accused of overstating the contribution of genetics to disease susceptibility (Geransar & Einsiedel, 2008), and it is likely that individuals with a better understanding of how genes, the environment and behaviors interact to affect disease risk may be more skeptical of the results of genetic susceptibility tests. In addition, the proposed model assumes that the credibility of genetic susceptibility tests will be a function of the setting of the test. Although the matter has been seldom examined, preliminary studies of university students show strong reluctance to pursue genetic testing through commercial providers compared to healthcare settings (Frysinger, Yashar, Christensen, Roberts, & Uhlmann, 2011). While many factors may explain this reluctance, it may be that the sustained criticism of experts has eroded public confidence about the credibility of the commercial testing industry. Alternatively, there may be an inherent reaction against commercialization of a product not usually offered in the marketplace.

THE DESIRE TO REDUCE UNCERTAINTY

Testing beliefs related to reducing uncertainty bear special mention in this model. As noted earlier, reducing uncertainty about disease risk is a hope many individuals cite while pursuing genetic susceptibility testing (Lerman, Seay, Balshem, & Audrain, 1995; Roberts et al., 2003). Three sources of uncertainty are of particular interest in the context of genetic susceptibility testing: uncertainty about the potential onset of disease in the future (*uncertainty about health*), uncertainty about whether risk perceptions are valid (*risk ambiguity*), and uncertainty due to the multiplicity of implications for the information (*complexity*).

Uncertainty about health has been long-recognized as an aversive state associated with negative emotions such as fear and anxiety (Lazarus & Folkman, 1984). In this perspective, genetic susceptibility testing might be conceptualized as a coping response, one that attempts to resolve the aversive state with information about disease risk. Yet, genetic susceptibility testing, by definition, can *never* objectively resolve uncertainty about health because it only provides information about greater or lesser risk for disease. For individuals who have sought testing with the belief that testing can resolve uncertainty about health, learning about its inability to do so is likely to be associated with lower test uptake through mechanisms involving fewer perceived informational benefits to testing (i.e., no resolution about uncertainty about health) and fewer perceived emotional benefits (i.e., no relief to the unease associated with a state of uncertainty). A direct effect on test follow-through is also likely, as uncertainty avoidance appears to be a well-established psychological process that might not be mediated by cognitions (Bechara et al., 1997).

Moreover, whether dropout occurs may also be a function of recruitment sources through pathways mediated by intrinsic and extrinsic motivation. The inability of testing to reduce uncertainty about health may matter only among those individuals who self-refer and feel strong intrinsic motivation to pursue testing. Among those who were systematically recruited and have greater extrinsic motivation, the uptake of testing is likely to be more contingent upon provider recommendations and perceived obligations than personal hopes to reduce uncertainty.

It is likely that many genetic research participants who hope to resolve uncertainty about health will follow through with testing. In these cases, the impact of testing beliefs involving reducing uncertainty about health are likely to mirror the impact of other types of risk assessments that don't provide deterministic information. The impact of disclosure upon health behavior changes among individuals who seek to reduce uncertainty about health are likely to be mediated by increases in negative affect attributable to the persistence of uncertainty and decisional regret about following through with testing. These emotional responses may also have a secondary effect on behavioral responses to disclosure by compromising the ability of individuals to process other information. Of note, negative affect such as anxiety or disease-specific worry is often associated with greater likelihoods of health behavior change (Witte & Allen, 2000), so the extent to which disclosure of probabilistic risk information creates or amplifies existing uncertainty about health may actually be associated with greater levels of health behavior change. Like test follow-through, negative emotional responses to learning that testing is not deterministic may be more powerful among those self-refer to testing as a result of feelings of greater personal responsibility for prolonging uncertainty. In contrast,

individuals who are systematically recruited may be more capable of dismissing unfulfilled hopes.

In contrast to uncertainty about health, the second form of uncertainty – *risk ambiguity* – is likely to be reduced through genetic susceptibility testing. Genetic susceptibility testing appears to have strong perceived credibility, demonstrated by its ability to change disease cognitions and emotions more than other established forms of risk assessments (Roberts, Cupples, Relkin, Whitehouse, & Green, 2005). Many have argued that genetics has been assigned power to predict future events with a certainty nowhere near the actual capability of testing (Nelkin & Lindee, 2004). These beliefs persist despite widespread concerns that genetic risk markers of questionable clinical validity have been incorporated into risk assessments in ways that convey a false sense of precision (Janssens & van Duijn, 2008).

The extent to which the desire to reduce risk ambiguity affects uptake of testing is likely to be a function about how test providers communicate the precision of the genetic risk assessment and the credibility assigned to genetic susceptibility testing. Pre-test educational approaches and genetic risk disclosure statements generally include some verbal or written acknowledgment of the limitations in current knowledge about the gene-gene, gene-environment, and gene-behavior interaction, among other complications. More elaborate textual and graphical approaches to communicating ambiguity, such as sharing confidence intervals or using histograms, introduce additional information that can compromise understandings and decrease trust in the information overall, though, particularly if individuals are less educated or have lower tolerance to ambiguity (Politi, Han, & Col, 2007). Education preceding testing often provides a preview of how genetic

susceptibility testing results will be communicated. The greater such education highlights a lack of precision to the risk information that would be produced, the more likely individuals will be to forego testing as a result of natural tendencies to avoid ambiguity.

Among those who follow through with testing, the format of the risk information is likely to affect cognitive and emotional responses as a result of resolving or exacerbating existing risk ambiguity. Interpretive labels that highlight whether individuals have a high, moderate, or low risk for disease, for instance, may resolve risk ambiguity among individuals who had no preconceived notions about their risk for certain conditions. Such individuals are likely to experience greater satisfaction with testing and may experience greater positive affect and less negative affect following results disclosure. On the other hand, individuals with strong family histories of disease, who already consider themselves at increased risk, may have been hoping for more precise quantification of their risk for disease and experience regret about testing and have negative affective responses to disclosure. Similarly, including confidence intervals in risk figures that graphically depict numerical risks may exacerbate risk ambiguity by highlighting the lack of precision to scientific information. The proposed model incorporates the impact of risk ambiguity by suggesting that the format of risk information presented both during pre-test information and genetic risk disclosure has a cognitive and emotional impact of risk presentation and contextualization of the information. Formats that emphasize the lack of precision in the scientific knowledge are likely to reduce the perceived credibility of the information and generate fewer positive affective responses and more negative affective responses.

A third type of uncertainty addressed in this model is complexity. As noted in the understanding section of the “Influence of Pre-test Education and Genetic Risk Communication” section, low genetic literacy combined with poor comprehensibility can compromise understandings and make the cognitive impact more contingent upon the perceived credibility of the source. The content of pretest education and genetic risk disclosure may also have an emotional impact by resolving or creating uncertainty related to the implications of the information on multiple outcomes. Pleiotropic effects of specific genes and gene-environment interactions were two important types of disease information identified in the literature review that may have been unanticipated by potential test recipients, and individuals may not fully consider the implications of genetic susceptibility testing for family members at the time of enrolling in a genetic susceptibility testing study. Genetic susceptibility testing has the potential of creating anxiety and unease as a result of its complexity and implications for others that does not exist as strongly for other types of risk assessment strategies. The proposed conceptual model recognizes that pretest education and genetic risk disclosure that includes disease information that addresses pleiotropy, gene-environment, gene-gene interactions or other family members is likely to increase uncertainty stemming from the complexity of the information. This uncertainty is likely to result in greater anxiety and unease.

SOCIAL SUPPORT AND SOCIAL NETWORKS

Although not central to explaining the impact of referral processes on behavioral outcomes, social support and the extent of a test recipient’s social network are included in the proposed model given their central role in numerous theories of health behavior and given the special role social support and social networks can play in the context of

genetic testing. Social support is defined as the quality of informational, emotional, instrumental and appraisal help individuals receive. It is a well-recognized determinant of behavior (Heaney & Israel, 2008) and has been incorporated into proposed models to predict responses to genetic susceptibility testing (Baum et al., 1997). Social networks are defined as the number of relationships an individual has and the reciprocity of those relationships (Heaney & Israel, 2008). Social support and social networks are consistently found to be characteristics of early adopters of innovations (Rogers, 2003), and are likely to be determinants of uptake of genetic susceptibility testing at the individual level, too. Moreover, social support and social networks are likely to be determinants of behavioral responses to genetic susceptibility test results. Genetic risk information does not have implications for individuals alone, but those who are related by blood; and Interdependence Theory asserts that even those who are not genetically related are influenced by the beliefs and attitudes of a genetic test recipient (Rusbult & Van Lange, 1996). The extent to which test providers connect test recipients to others may determine the degree to which group-level behavior change is pursued.

LIMITATIONS OF THE PROPOSED MODEL AND GAPS IN KNOWLEDGE

The preceding literature review and description of a conceptual model emphasize a number of important gaps in the literature. First, our knowledge of susceptibility testing is based largely on literature from single-disease susceptibility testing that examined individual genes. While disease-specific factors often drove use of and response to such tests, they're likely to be less important in the context of the current generation of susceptibility tests. Not only is single-gene, single-disease testing far more focused than the multi-disease, multi-gene panel tests that characterize what's emerging primarily, but

it also tends to include genes whose predictive power far exceeds those of panel tests (although the introduction of markers with greater predictive power into consumer panels, such as *APOE* for AD, is starting to occur). Despite the many caveats described, the model may overemphasize the role of illness perceptions. For instance, while risk perceptions are important predictors of use of many susceptibility tests with strong predictive power, it was not predictive of uptake of testing in the Multiplex Initiative which incorporated markers with lower predictive power (McBride et al., 2009). What's more, the proposed model may oversimplify many constructs and the relationships between them. A recent analysis of data from the Multiplex Initiative using structural equation modeling found important differences regarding perceptions of metabolic conditions like hypercholesterolemia and type two diabetes; and cancer syndromes including colorectal, skin and lung cancer (Wade et al., 2011). Moreover, testing beliefs (specifically, response efficacy beliefs about testing rather than health behaviors) were a function of severity perceptions, worry, and susceptibility perceptions (Wade et al., 2011). These relationships need to be taken into consideration as future studies are developed.

In addition, the conceptual model developed here draws strongly from research that enrolled mainly Caucasians, particularly those with higher educational attainment and household incomes. The model proposed here argues for greater sensitivity to differences in decision-making preferences, yet it positions decision-making preferences and motivational context within a framework developed from studies that enrolled participants likely biased towards autonomous decision-making preferences. The factors that promote and inhibit optimal health behaviors often differ greatly for different groups.

For instance, parental approval and disapproval of smoking appears to have a much stronger influence among African Americans than Caucasians (Clark, Scarisbrick-Hauser, Gautam, & Wirk, 1999). Conversely, peer-pressure smoking cessation interventions work better among Caucasians than African Americans (Griesler & Kandel, 1998). These differences reflect underlying and deeply-rooted differences in the strength of social influences and individual cognitive factors that may differ by population. The narrative of genomics as a component of ‘personalized medicine’ and ‘empowerment’ may frame genetic susceptibility testing in ways that are asynchronous with the way different populations approach health. What’s needed is not only a diversification of study populations, but greater sensitivity to how different populations approach health.

This point raises a third gap: the overwhelming majority of research on genetic susceptibility testing has examined uptake of testing and behavioral responses as functions of individual-level factors. Important interpersonal and upstream factors are neglected in the literature and have been omitted from the proposed model. Examples include educational policies that emphasize or de-emphasizes science and genetics and ultimately shape understandings, beliefs, and perceptions; payer policies that affect reimbursement for genetic services and access to genetic counseling; and most notably, health policies and ideological environments that conceptualize health as the responsibility of individuals rather than communities or societies that heighten fears about discrimination and establish contexts that either align or conflict with autonomous or paternalistic decision-making preferences. Such factors may explain why Americans, with their emphasis on individual responsibility for health, rate the ability of genetic testing to help when making later-life decisions and planning for the future – as well as

the possibility of insurance and employment discrimination – much higher than, for example, Italians, who receive healthcare in a public system that assures coverage for all (Binetti et al., 2006). Given the implications of an individual's genetic test results for his or her relatives, familial factors, at the least, may be important next steps in this area of research.

Lastly, little attention has been devoted to the psychosocial implications of genetic susceptibility testing as an emerging technology. Work on the diffusion of innovations consistently shows that the demographic profiles and attitudes of those who are early adopters of a new technology are very different from demographic profiles and attitudes of those who are later adopters (Rogers, 2003). Genetic susceptibility testing for conditions such as hereditary breast and ovarian cancer and Lynch syndrome have been available for almost two decades. An understanding of how attitudes towards testing for those conditions have changed over time may provide insight about how well the proposed model may apply to future generations of test seekers.

CONCLUSIONS

The literature review in Chapter 3 and the conceptual model proposed here highlight the important role referral processes may play in determining who enrolls in genetic susceptibility testing research, how likely they are to follow through with testing, and how frequently they engage in health behavior changes afterwards. The kinds of populations that enroll in genetic susceptibility testing research through self-referral are likely to differ greatly from the populations that seek genetic susceptibility testing through systematic recruitment: self-referred individuals are likely to have greater motivation for testing as a result of cognitions shaped by factors such a personal or

family history of disease. More specifically, self-referral strategies likely enroll populations with stronger overall beliefs about the ability of testing to satisfy perceived needs, stronger beliefs in the ability of health behaviors to reduce disease risks and greater self-efficacy towards those behaviors. Self-referred study populations may also perceive greater susceptibility to disease and may consider genetics to play a stronger role in disease causation, although such associations are less likely in the context of multi-gene, multi-disease panel tests examining markers with low penetrance.

The likelihood that participants of genetic susceptibility testing research actually follow through with testing also depends on whether they self-referred or were systematically recruited. Differences in cognitions based on who enrolled play a role; but referral processes may also alter the cognitive and affective impact of pre-test education as well as affecting the motivation participants have to pursue testing. Similarly, referral processes may additionally affect behavioral responses by affecting the locus of their motivation to pursue health behavior changes and the way they interpret genetic risk information cognitively and emotionally. Referral processes not only affect who enrolls in genetic susceptibility testing research, but also how those participants interpret information provided during the testing process and whether they are intrinsically or extrinsically motivated to follow through with genetic risk disclosure and pursue health behavior change.

An improved understanding about how recruitment methods affects enrollment in genetic susceptibility testing research, uptake of testing, and responses to genetic susceptibility testing has important implications for the ways genetic testing is regulated and the way it may be used as a public health tool. It is possible that testing could become

an important part of health promotion strategies if testing was offered in ways that maximized empowerment and motivation for health behavior change. There is also a need to recognize that genetic susceptibility testing may never achieve the level of motivational power that proponents initially envisioned, and that the use of self-referral recruitment strategies in many genetic susceptibility testing studies has the potential to inflate the ability of testing to result in healthier lifestyles. The preceding literature review and conceptual model serve as a foundation for the analyses in Chapters 4 through Chapter 6.

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CHAPTER 4
DIFFERENCES IN BASELINE DEMOGRAPHICS
AND PSYCHOSOCIAL PROFILES

BACKGROUND

Genetic susceptibility testing generates excitement for its potential to help promote adoption of preventive behaviors, aid in long-term health-related planning, and provide psychological benefits (Botkin et al., 2010; Collins, Green, Guttmacher, & Guyer, 2003; Evans, 2007). Research to date shows that the emotional risks of testing provided by expert clinicians are minimal, with long-term distress being rare (Broadstock, Michie, & Marteau, 2000; Douma, Aaronson, Vasen, & Bleiker, 2008; Hamilton, Lobel, & Moyer, 2009). Results from behavioral research have been mixed, however, with rates of test uptake and health behavior change varying greatly from study to study (McBride, Koehly, Sanderson, & Kaphingst, 2010; Ropka, Wenzel, Phillips, Siadaty, & Philbrick, 2006; Smerecnik, Grispen, & Quaak, 2012). Identifying factors that affect who follows through with testing and how they respond to its results is critical to understanding under what conditions, if at all, genetic susceptibility testing can be an effective health promotion tool. Although differences in test factors (e.g., accuracy, predictive power), disease factors (e.g., preventability, treatability), and outcomes of interest (e.g., smoking cessation, physical activity) likely account for much of this

variation, just as important may be the way individuals learn about and initiate the process of testing.

One important distinction may be whether or not participants self-refer to testing services. Self-referral can be defined as situations where individuals initiate contact with researchers, whereas systematic recruitment can be defined as situations where individuals enroll in response to invitations from researchers. Many notable studies of genetic susceptibility testing have examined samples enrolled primarily through self-referral. Such strategies have been criticized because they provide no information about non-participants, making it nearly impossible to draw conclusions about how representative data is for a broader population and therefore limiting the ability to infer what may occur if testing is made available in ways more appropriate for population-level intervention, like primary care settings (McBride et al., 2010). In addition, the profile of the participants they enroll may differ in important ways from the profile of participants enrolled through systematic recruitment. Self-referred cohorts have tended to be younger (DeBar et al., 2009; Snyder et al., 2008), have stronger family histories for disease (Henrikson, Harris, & Bowen, 2007), and are often less healthy (DeBar et al., 2009; Henrikson et al., 2007; Snyder et al., 2008) than cohorts enrolled through systematic referral processes like targeted mailings or physician referrals. In addition, self-referred populations tend to be more motivated for behavior change (Binks & O'Neil, 2002), have greater self-efficacy about preventive health behaviors (Snyder et al., 2008), stronger beliefs that genetics can increase risk for disease (Henrikson et al., 2007), and greater levels of depression and anxiety (Henrikson et al., 2007) than systematically

recruited populations. These differences can be important given their frequent associations with preventive health behaviors.

Furthermore, the process of self-referral may itself affect how individuals respond to an intervention. Self Determination Theory suggests that situations that promote autonomy increase intrinsic motivation (Ryan & Deci, 2000). Contexts where individuals must initiate action rather than respond to invitations, like self-referral to interventional research, may actually lead individuals to have greater intrinsic motivation for action. More explicitly, self-referral may set a precedent where participants are proactive rather than reactive about decisions regarding testing and health behavior change. Due to the general lack of clinical utility in genetic susceptibility testing for common disease, providers are at most nondirective (if not discouraging) about whether individuals should follow through with testing or change health behaviors in response to results. If self-referral does prime individuals to act without being directed, then individuals who self-refer to testing services may be more likely to actually follow through with testing or to initiate health behavior changes than individuals who are enrolled through systematic recruitment.

Despite its potential impact on study outcomes, few analyses have explored the implications of self-referral to genetic susceptibility testing research. Apolipoprotein E (*APOE*) genotyping for Alzheimer's disease (AD) risk provides an opportunity to address this gap in the literature. AD is the most common form of dementia among the elderly, affecting about five million Americans (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). One of the most common risk factors for AD is the $\epsilon 4$ allele of the *APOE* gene, carried by at least 20% of individuals in most population groups (Corbo & Scacchi,

1999). *APOE* encodes for apolipoprotein E, a lipid transport protein with three main forms, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The $\epsilon 4$ allele increases the odds of developing by approximately 2.5 to 15-fold, depending on the number of $\epsilon 4$ copies, ethnicity, and sex (Farrer et al., 1997). However, as with any genetic susceptibility marker, the $\epsilon 4$ allele is neither necessary nor sufficient for the development of AD. Numerous consensus statements issued in the 1990s strongly discouraged AD susceptibility testing using *APOE* due to limitations in the predictive value of testing and a lack of proven AD prevention options (Brodaty et al., 1995; McConnell, Koenig, Greely, & Raffin, 1999; NIA/Alzheimer's Association Working Group, 1996). Recent guidelines issued jointly by the American College of Medical Genetics and the National Society of Genetic Counselors have taken a softer stance, asserting that “testing may be considered at the clinician’s discretion” (Goldman et al., 2011, p. 601). Nevertheless, clinical settings still rarely conduct genetic susceptibility testing using *APOE*.

This paper examines how self-referred participants in the second and third trials of the Risk Evaluation and Education for Alzheimer Disease (REVEAL) Study compare to systematically recruited participants both demographically and on psychosocial factors that may be predictive of test uptake and health behavior change following disclosure of results. Since 1999, the REVEAL Study has offered genetic risk assessments for AD based on *APOE* genotyping to healthy adults in an effort to improve understandings about how individuals seek testing, what affects whether individuals follow through with genotyping, and how test recipients respond behaviorally and psychologically to results. An analysis of data from the study’s first trial, conducted from 1999 to 2003, found that self-referred participants were, at intake, more likely to be female, more educated, and

younger than systematically recruited participants (Roberts et al., 2004). The analyses presented here build on those findings by examining demographic differences among the cohorts that enrolled between 2003 and 2009, and by also focusing on differences on key psychosocial factors that are not only predictive of test uptake, but also likely correlates of changes in preventive health behaviors, long-term health-related planning, health information seeking, and psychological wellbeing after receipt of test results.

Hypotheses about demographic factors assume that demographic differences between self-referred and systematically recruited participants in the first REVEAL Study trial noted above will be observed in the second and third trials. In addition, hypotheses further assume the cohort of self-referred participants is more likely to have characteristics associated with test uptake or research participation in other contexts. Demographic trends noted in the literature on genetic susceptibility testing and clinical research suggest that participants who seek information about testing (but do not necessarily follow through with it) are less likely to self-identify as minorities (Alford et al., 2011; Ford et al., 2006; McQuillan, Porter, Agelli, & Kington, 2003; Murthy, Krumholz, & Gross, 2004), and have stronger family histories of disease (Henrikson et al., 2007; Ropka et al., 2006).

Hypothesis 1: Self-referred participants are more likely to be female, Caucasian, younger, of higher socioeconomic status, and have stronger family histories of AD than systematically recruited participants.

Hypotheses about psychosocial factors likewise assume that the cohort of self-referred participants is more likely to hold beliefs and perceptions associated with hypothetical

and actual test uptake. Table 2 presents a listing of constructs that have been found in other studies of genetic susceptibility testing to be associated with uptake of actual or hypothetical testing. Based on those findings, the secondary analyses presented here test the following hypotheses about cognitive and emotional differences between referral cohorts:

Hypothesis 2a: Self-referred participants have stronger beliefs about the benefits of testing, the efficacy of health behaviors to prevent AD, greater perceived susceptibility to AD, stronger beliefs that genetics causes AD, and greater coping self-efficacy than systematically recruited participants.

Hypothesis 2b: Self-referred participants have greater pretest AD concern and worry than systematically recruited participants.

METHODS

Overview

I conducted a secondary analysis of data from the second and third trials of the REVEAL Study, a series of multicenter randomized clinical trials examining the psychosocial and behavioral impact of providing AD susceptibility testing with *APOE* genotype disclosure (see Roberts (2011) for a summary of findings). The first REVEAL Study trial (1999-2003) compared the impact of genetic risk assessment for AD against a risk assessment for AD based on family history and gender. The second trial (2003-2006) was built on work from the first by expanding the participant profile to include more African Americans and by testing a condensed educational and counseling protocol against an extended model based on genetic testing for cancer susceptibility. The third

trial (2006-2009) explored the impact of disclosing that the $\epsilon 4$ allele of *APOE* is associated with coronary artery disease in addition to AD, and also tested a telephone disclosure protocol against in-person disclosure. In each trial, study sites decided individually how to recruit participants. Preliminary analyses of the primary study aims of the second and third trials have been presented elsewhere (Christensen, Roberts, Uhlmann, Whitehouse, Obisesan, Cupples, et al., 2010; Christensen, Roberts, Uhlmann, Whitehouse, Obisesan, Bhatt, et al., 2010; Green et al., 2006; Roberts et al., 2008) and are being reported separately.

Sites participating in the second trial included the Boston University School of Medicine in Boston, MA; Case Western Reserve Medical School in Cleveland, OH; the Weill School of Medicine in New York, NY; and the Howard University School of Medicine in Washington, DC. The third trial included the same sites, except the University of Michigan School of Public Health in Ann Arbor, MI replaced the Weill School of Medicine.

Procedures

Multidisciplinary teams of experts in the fields of AD, neurology, genetics, genetic counseling, health behavior, psychology, and bioethics created protocols in each trial. An External Advisory Board, as well as institutional review boards at each of the study sites, oversaw development and provided final approval. Figure 3 presents a study flow chart with sample sizes at each stage stratified by referral process. Following intake, participants provided informed consent for the parts of the study that preceded the blood draw for genotyping (separate written consent was obtained at the time of the blood draw for genotyping for the remaining parts of the study). Participants then completed a

telephone interview followed by a self-administered mailed questionnaire. Upon return of the mailed questionnaire, participants received pretest education in one of two forms: through an in-person educational session with a genetic counselor followed by a separate genetic counselor-directed discussion at the time of the blood draw (2nd trial, control arm) or through mailed educational brochures followed by participant-directed question-and-answer at the time of the blood draw (2nd trial, experimental arms; all 3rd trial participants). A genetic counselor, physician or health educator then disclosed *APOE* genotypes and numerical risk assessments through age 85, and REVEAL researchers followed participants for the period of one year. Given the focus of this paper on potential differences in study populations introduced by self-referral, analyses presented here will use only data collected at intake, in the phone interview, or through the mailed questionnaire administered prior to the education step.

Participants and recruitment

Inclusion criteria varied by REVEAL Study trial. Participants in the second trial were adult first-degree relatives (FDRs) (i.e., child, sibling or parent) of a living or deceased patient with AD. In the third trial, that criterion was relaxed slightly, and individuals with no affected FDRs were enrolled as well as individuals with a single FDR. Individuals in both trials for whom the average age of onset of AD within the family was 60 years or less were excluded due to the potential that they may be carriers of mutations to other genes (*PS1*, *PS2*, or *APP*) associated with early-onset AD that were not examined in the REVEAL Study. Individuals in both trials with two or more affected FDRs were also excluded from participation because risk models for them could not be developed with sufficient precision. Finally, individuals in the third trial who did not self-

identify as either Caucasian or black/African American were excluded at most study sites because of concerns that risk models have questionable validity for other ethnic groups.

Study sites independently decided how to recruit participants. Nearly all sites used a combination of approaches. Active, targeted efforts to enroll individuals with an interest in research or dementia included mailings to participants of research registries, in-person recruitment in the wait areas at neurology clinics, referrals from collaborating physicians, and mailings to individuals who had participated in other AD-related studies. Untargeted efforts included advertisements in local newspapers, flyers posted in clinics, and presentations about the study at community centers. Passive approaches included postings on research-related websites (e.g., clinicaltrials.gov, the Alzheimer's Disease Education and Referral Center), and word-of-mouth. To ensure demographic diversity in the second trial, the study team established a target to enroll roughly equal numbers of adults under the age of 60 and 60 or older. Similarly, the third trial had enrollment quotas by site such that the final sample would have an even proportion of males and females; an even proportion of individuals 60 or older and less than 60 years of age; and $\frac{3}{4}$ would have a single AD-affected FDR while $\frac{1}{4}$ would have no AD-affected FDR. In both trials, the study team relaxed quotas near the end of the recruitment period to better ensure that overall enrollment numbers would satisfy statistical requirements.

Measures

Referral process

During intake, a research coordinator or research assistant queried participants about how they “heard about the REVEAL Study.” The coordinator or assistant then categorized verbal responses at the time of data collection into one of seven major

response categories, described below. With help from the overall project managers of the second and third trials, I classified these categories as systematically recruited or self-referred depending on who initiated contact. REVEAL Study personnel initiated contact with systematically recruited participants, whereas self-referred participants initiated contact with the REVEAL Study.

Coded as systematically recruited

1. *From another research study at this hospital (n=149).* Study personnel coordinated with researchers specializing in neurology and AD and encouraged them to discuss the REVEAL Study when appropriate. Examples include individuals who completed the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) examining the impact of anti-inflammatory medicines on AD risk (ADAPT Research Group, 2008); and individuals who agreed to donate their brains to AD research centers upon their death.
2. *Someone from the study talked to me in the waiting room (n=6).* Study personnel approached families in waiting areas of neurology and geriatrics clinics to explain the goals and steps of the research, and to attempt to enroll interested individuals.
3. *Someone from the study called me at home or work (n=35).* Study personnel cold-called individuals whose provided telephone information for research purposes, usually as part of their participation in a research registry.

Coded as self-referred

4. *From a brochure or advertisement (n=233)*. The research team created site-specific recruitment brochures and left them in locations where individuals with an interest in AD research might encounter them (e.g., the waiting rooms of neurology clinics). In addition, advertisements in local newspapers or posted flyers in strategic locations (e.g., clinics) provided information about the aims and methods of the study as well as a phone number and email address for interested individuals to use to initiate contact with REVEAL Study personnel. Appendix 1 presents samples of recruitment brochures and advertising text.
5. *Someone from the study gave a presentation (n=49)*. REVEAL Study personnel presented information about the study in the context of raising awareness about AD at community events (e.g., at public libraries). Study coordinators classified attendees in this category if they provided intake information at the event or if they contacted the study afterwards.
6. *From a friend (n=45)*. These individuals learned about the REVEAL Study from an acquaintance (e.g., a friend or co-worker) who was either a participant or had heard about the study another way, usually in the media (e.g., newspaper article, news report), and then initiated contact with a REVEAL Study coordinator.

Coded after further analysis

7. *Other*. At intake, the study coordinator or research assistant tagged individuals who didn't fit into the prior six categories as "other" and wrote descriptions. I

recoded these descriptions into the following subcategories, after discussion with the primary project managers of the second and third REVEAL Study trials:

Coded as systematic recruitment

- a. *Alzheimer's Disease Center referral (n=7)*. These individuals contacted the Boston University Alzheimer's Disease Center and either wanted to participate in another study that was closed or for which they did not qualify; or accompanied an AD-affected relative to a research appointment for another study and were invited to participate. In both cases, participants did not have prior knowledge about the REVEAL Study.
- b. *Clinic intake (n=12)*. Howard University personnel classified individuals they approached at neurology clinics in this subcategory.
- c. *Provider referral (n=25)*. These individuals identified a specific nurse, physician, or genetic counselor who provided them information about the REVEAL Study.
- d. *Mailing (n=15)*. These individuals responded to a paper-based or electronic mailing sent to them because they had participated in ADAPT, because they were members of the Michigan Alzheimer's Disease Research Center research registry, or because they were a member of the Dementia Coalition in Michigan.

Classified as self-referral

- e. *Heard from family/friend/participant (n=37)*. These individuals mentioned a specific individual (family member, friend, or a participant already in the study) who told them about the REVEAL Study.
- f. *Media (n=91)*. These individuals read about the REVEAL Study in a newsletter (e.g., Long Island Alzheimer's Foundation newsletter), newspaper article (e.g., *Ann Arbor News* press release), a book (e.g., *Carved in Sand*), or heard about it at an event (e.g., a Memory Walk) and found information about how to contact the REVEAL Study.
- g. *Self-referred (n=3)*. Study personnel tagged some individuals as "self-referred" without further elaboration.
- h. *Web site (n=64)*. These individuals either i) heard about the study in some unspecified manner and found a website created at one of the participating study sites; ii) visited a news or entertainment website that was discussing the REVEAL Study, such as *USA Today* online; iii) found REVEAL Study details on a website dedicated to helping studies enroll participants (e.g., *clinicaltrials.gov*, the University of Michigan ENGAGE website); or iv) said they had learned about the study "online," "on the internet," or through a "Google search" without being specific and initiated contact with study personnel.
- i. *Health fair (n=10)*. These individuals learned about the REVEAL Study by approaching a booth set up at a health fair by study personnel from Howard University.

- j. *Wait list from prior trial (n=10)*. Boston University waitlisted individuals who self-referred and wanted to participate in the first REVEAL Study trial but were excluded due to lack of space. Researchers invited them to participate in the second trial.

Demographics

Participants self-reported age, gender, race, and number of family members with AD at intake and reconfirmed that information during the phone interview or at the blood draw session. Racial groups were classified as “black/African American” and “other” in these analyses because individuals self-identifying as black or African American received one set of AD risk estimates and individuals self-identifying in any other racial category received a separate set of AD risk estimates (note: individuals who self-identified as neither white/Caucasian nor black/African American were excluded from enrollment in the third trial at most sites. See the Participants and Recruitment section for an explanation). In addition, participants self-reported years of education, total household income (response options: <\$10K, \$10-29K, \$30-49K, \$50-69K, \$70-\$99K, \$100K+, refuse to answer), and employment status (full-time, part-time, unemployed, or retired) during the telephone interview. Study records provided information about study site and trial round (second or third trial), as well as *APOE* genotype which was dichotomized depending on whether a participant carried at least one copy of the *APOE* ϵ 4 allele associated with increased risk for AD or not. Of note, three individuals who completed intake but didn’t proceed further in the study did not specify a race, one did not provide gender information, four did not specify age, and eleven did not specify the number of affected relatives. Thirty seven who completed the phone interview either skipped or

declined to provide household income information, and one individual failed to provide employment information. No data was missing about education.

Cognitions

Interest in genetic test. A single item at intake asked “in general, do you think you would be interested in having a genetic test to assess your chance of developing AD?” Response options included yes, no, and maybe. Item non-response was minimal (3 instances among those who did not proceed past intake).

Perceived AD susceptibility. A single item that differed slightly by REVEAL Study trial assessed perceived AD susceptibility. In the second trial, participants verbally responded to the question, “on a scale of 0 to 100%, what do you think your chance of developing AD during your lifetime is?” In the third trial, participants verbally responded to the question, “out of 100 people just like you, how many of them do you think will develop Alzheimer’s disease in their lifetime?” The written questionnaire repeated each item. Non-response totaled 12 instances at intake and 10 instances in the mailed questionnaire.

In addition, the written questionnaire assessed perceived AD susceptibility a second way using an analog measure where participants responded to the item, “Place an ‘x’ on the part of the scale that best describes your chance of developing Alzheimer’s disease.” A research assistant converted responses to a 0-100% numeric value depending on the placement of the ‘x’ on a line ranging from “no chance” to “certain.” The susceptibility measure at intake correlated strongly with both the measure administered in the mailed questionnaire ($r=.663$, $p<.001$) and the analog scale ($r=.442$, $p<.001$) and

generated comparable results during data analysis. As a result, this paper summarizes only data from the intake measure to simplify presentation of analyses.

Perceived AD seriousness. A single item administered at intake asked to rate their agreement to the statement “Alzheimer disease is the worst disease I can think of” on a 5-point scale from strongly disagree (1) to strongly agree (5). Non-response at intake (1 instance) occurred for one participant who was neither self-referred nor systematically recruited.

Perceived benefits and perceived risks and limitations. The written questionnaire measured *perceived benefits* and *perceived risks and limitations* of genetic susceptibility testing for AD using scales developed from research on genetic testing for hereditary breast and ovarian cancer and implemented in subsequent studies of attitudes about AD susceptibility testing, including the first REVEAL Study trial (Lerman et al., 1996; Lerman, Seay, Balshem, & Audrain, 1995; Roberts et al., 2003). Questionnaires included a section that offered eleven reasons “why someone might take a genetic test for AD” (benefits), such as “to seek information on preventative measures,” “the need to make arrangements for my long-term care,” and “curiosity.” A separate section offered ten reasons “why someone might not want to take a genetic test for AD” (risks and limitations), such as “there is no way to cure or prevent AD,” “the test does not give me a definite answer about whether I might get AD or not,” and “the results could affect my health insurance.” Participants rated the importance of each reason to them on a scale of 1 (not at all) to 5 (extremely).

Item non-response was minimal on most items (up to 10 instances per item) except for two items specific to children. Twenty-one participants did not provide a rating

on, “to give information about my children’s possible risk of AD,” and 19 did not provide a rating on, “it could make me worry about my children's risk of getting AD.”

I averaged numerical responses on each scale to create summary benefits and risks and limitations scores ranging from 1-5 each. Internal consistency was strong for each measure: Cronbach’s alpha was .83 for the benefits scale and .81 for the risks and limitations scale.

Coping self-efficacy. During the telephone interview, participants rated their certainty that they would be able to cope with receiving a genetic test result that indicated an increased chance of developing AD, with 0% being certainty that they could not cope and 100% being certainty that they could cope. Three participants did not respond to this item, including two who did not progress further into the study.

Causal beliefs. Items assessing causal beliefs were replicated from research on AD illness representations (Roberts & Connell, 2000). The written questionnaire assessed *genetic causal beliefs* with a single item where participants rated the importance of “genetics/heredity” for increasing one’s risk of AD. Scores ranged from 1 (not important) to 5 (very important). Similarly, a measure of *lifestyle causal beliefs* asked participants to rate the importance of “lifestyle (e.g., diet, exercise, smoking)” in increasing one’s risk of AD, also on a 1-5 scale from not important to very important. Three participants who completed the mailed questionnaire failed to respond to the genetic causal belief item, and four failed to respond to the lifestyle causal belief item.

AD control. Measures in the written questionnaire assessing AD control beliefs differed by REVEAL Study trial. In the second trial, participants rated their agreement from 1=strongly disagree to 5=strongly agree with four statements adapted from the

Multidimensional Health Locus of Control Scale (Wallston & Wallston, 1978): “no matter what I do, if I am going to get AD, I will get it,” “if I take care of myself, I can avoid AD,” “there are medicines, foods, or personal behaviors that can reduce severity of AD,” and “if I have a form of a gene that increases my risk for AD, I can take actions that will help prevent it.” In the third trial, participants rated their agreement using the same response options with six statements adapted from the Revised Illness Perceptions Questionnaire (Moss-Morris et al., 2002): “there is a lot the person can do to control his or her symptoms of AD,” “what the person does can determine whether his or her AD gets better or worse,” “the course of the Alzheimer’s disease depends on the person,” “nothing the person does will affect his or her Alzheimer’s disease,” “the person has the power to influence his or her Alzheimer’s disease,” and “the person’s actions will have no effect on the outcome of his/her Alzheimer’s disease.” Summary measures were created by averaging responses to scale items (reverse scoring where appropriate) and standardizing the scores.

Item non-response was minimal on these items (no more than 2 instances on any single item in either trial). Internal consistency of the scale used in the second trial was borderline (Cronbach’s $\alpha = .65$), but strong for the scale used in the third trial (Cronbach’s $\alpha = .80$).

Emotional factors

AD concern. The intake instrument assessed AD concern using a scale implemented in prior research on FDRs of AD patients (Roberts & Connell, 2000). Participants rated their agreement on 5-point scales on the following four items: “I am concerned that I will develop AD,” “I am concerned that I will develop Alzheimer

disease in the next 5 years,” “I would like to know if I am going to develop AD at some point later in my life,” and “I believe that I will someday develop AD.” A fifth scale item (“AD is the worst disease I can think of”) was dropped due to poor corrected item-total correlation ($r=.23$). Item non-response was negligible (3 instances). Internal consistency of this scale was borderline (Cronbach’s $\alpha = .65$).

AD worry. During the phone interview, a single item asked, “Presently, how often do you think about getting Alzheimer's disease?” Participants responded on a 4-point scale from 1=not at all/rarely to 4=a lot. Two participants failed to respond to this item.

Data analysis

Missing data for individuals who retained through completion of the mailed questionnaire (henceforth referred to as the “retained sample”) was imputed through fully conditional specification, also known as multivariate imputation by chained equations, using R package *mice 2.12* (van Buuren & Groothuis-Oudshoorn, 2011). Models for each imputed variable included the following predictors: referral status, demographic characteristics, baseline cognitions and emotions of focus in these analyses, and stage of study dropout. I ran 20 iterations to create 5 imputed datasets, and used rules developed by Rubin (1987) to pool estimates and variances from imputed datasets and rules developed by Meng and Rubin (1992) to conduct Wald tests to compare linear regression models and likelihood ratio tests to compare logistic regression models. All analyses were conducted using R version 2.15.0 for Windows (R Development Core Team, 2011).

I tested for differences on demographic variables by referral cohort using independent samples t-tests on continuous variables (age and education), 2-proportion tests on race and gender, chi-squared tests on the balance of categorical variables

(employment status, $\epsilon 4$ carrier status, site, and trial), and Wilcoxon rank sum tests on highly skewed or ordinal variables (family history and income, respectively). Where hypotheses existed (age, education, race, gender, family history, and income), I used one-sided tests. I used two-sided tests to explore differences on all other demographic variables. I used the same statistical procedures when exploring bivariate associations between demographic variables and study dropout before completion of the written questionnaire, including two-proportion tests for referral process. Logistic regression examined the independent effects of demographic factors on study attrition. One-sided 2-proportion tests examined the hypothesis that the self-referred cohort had greater interest in testing, and one-sided independent samples t-tests examined the hypotheses that perceived AD susceptibility, AD concern and worry, genetics and lifestyle causal beliefs, and AD control beliefs would all be greater among the self-referred cohort. I compared the perceived benefits of testing against perceived risks and limitations and compared genetics causal beliefs against lifestyle causal beliefs using paired t-tests. Finally, I used linear regression to test hypotheses related to the same set of psychosocial factors after controlling for demographic factors found to differ by referral process in bivariate analyses. All analyses were conducted using R version 2.15.0 for Windows (R Development Core Team, 2011).

Of note, study records were insufficient to calculate response rates among the systematically recruited population. One of the strengths of the REVEAL Study is its use of randomization and control groups to test primary study hypotheses and maximize internal validity. Less attention has been devoted to external validity, given enrollment of self-selected samples that are clearly unrepresentative of the population at-large.

Consequently, information that would permit calculation of response rates, such as how many recruitment packages were mailed to research registry members or how many families were solicited in the wait areas of clinics, were not tracked.

RESULTS

Intake by referral process and dropout by mailed questionnaire

Table 3 summarizes how 817 individuals completing intake learned about the study. The self-referred cohort outnumbered the systematically recruited cohort in the second and third trials (61% vs 36% of total study participants in the second trial, 74% vs 24% in the third). Nearly half of self-referred participants reported learning about the study from a brochure or advertisement, whereas the majority of systematically recruited participants reported referral from another research study at the same institution. Across trials, 22 individuals (3%) were missing data about how they learned about the study and were omitted from further analyses.

Of note, quotas used in both trials meant that many individuals fitting specific demographic profiles could not enroll in the study. Sites did not formally track interested individuals who were unable to participate, but data from the University of Michigan site suggest 100 women were denied the opportunity to participate because the site had already met specific gender-age-family history targets, compared to only 19 men; and anecdotal evidence suggests that individuals denied enrollment into the second trial due to filled quotas were predominantly female. All denied individuals had self-referred to the study.

Also noteworthy were lower rates of study dropout among the self-referred cohort, even at the earliest stages of the study. Nearly double the proportion of

systematically recruited participants who completed the phone interview failed to complete the pre-education written questionnaire compared to the self-referred cohort ($\chi^2=23.2$, $p<.001$).

Sample demographics at intake and of the retained sample

Table 4 presents the demographic profile of the self-referred and systematically recruited populations at each measure's earliest data collection point (in general, at intake). As predicted, the self-referred sample was younger, less likely to self-identify as black or African American, tended to have higher household income, and had more relatives on average affected by AD than the systematically recruited sample. In addition, the self-referred cohort was more likely to be employed part or full time than the systematically recruited cohort, although retirees largely drove this difference: 39% of the systematically recruited cohort reported being retired compared to 22% of the self-referred cohort.

Data did not support hypotheses related to gender and education. Regarding gender, far more women enrolled overall than men, but differences in the analyzed samples did not reflect differences by referral cohort. However, sub-analyses examining gender in the second trial found a greater proportion of women in the self-referred cohort than the systematically recruited cohort (75% vs 66%, $\chi^2=3.84$, $p=.025$). Sixty-nine percent of participants reported education levels equivalent to a bachelor's degree or higher. Differences by referral cohort were not apparent.

Study sites contributed participants to each cohort in different proportions. Whereas just less than half of participants from the Boston University site were self-referred, 65% to 92% of participants enrolled at other sites were self-referred. The second

and third trials also contributed differently to each cohort, as noted earlier. Table 5 summarizes the characteristics the retained sample and those who dropped out before completing that step, stratified by referral process. Bivariate analyses found that black participants were less likely to be retained in the study and to complete the mailed questionnaire, at least among the systematically recruited cohort (systematically recruited: $\chi^2=5.7$, $p=.017$; self-referred: $\chi^2=2.2$, $p=.135$). Disparities also existed by study site, at least among the self-referred cohort (systematically recruited: $\chi^2=5.8$, $p=.234$; self-referred: $\chi^2=32.2$, $p<.001$). In fact, while differences in attrition before completion of the pre-education questionnaire remain significant by site in multivariable analyses using logistic regression (Wald test $\chi^2=18.1$, $p=.001$), differences by race disappear altogether in multivariable analysis using logistic regression. Table 6 summarizes results of that multivariable model.

Baseline psychosocial measures

Table 7 summarizes measures of psychosocial constructs stratified by referral cohort and study retention through completion of the mailed questionnaire. Interest in testing was extremely high among all groups at intake, with less than 1% of the self-referred cohort and 4% of the systematically recruited cohort reporting no interest. Differences in interest were not large, but still statistically significant. As hypothesized, AD worry was greater at intake among the self-referred cohort in bivariate analyses, with 20% of self-referred participants reporting thinking about getting AD not at all or rarely compared to 32% of the systematically recruited cohort. AD concern was also greater among the self-referred cohort, with 72% of self-referred participants scoring greater than 3 (tending to agree with concern items) compared to 64% of systematically recruited

participants. Findings on AD worry did not change when adjusting for baseline differences in demographics, but AD concern was marginally non-significant in multivariable analyses. See Table 8.

Cohort differences were even fewer when examining only the retained sample. Cohort differences in interest in testing were not different in bivariate analyses of the retained sample, as 21 of the 36 participants (58%) who responded “maybe” as their interest dropped from the study before completing the mailed questionnaire, and an even higher percentage who responded “no” (10 of 14, 71%) were lost by that stage. Differences in AD concern were also marginally non-significant in bivariate analyses when examining only the retained sample, as participants with less concern were more likely to drop out (mean among dropouts = 3.29, mean among retained sample = 3.47, $t=2.87$, $p=.004$).

Analyses showed no differences by referral cohort on all other psychosocial factors. Average AD susceptibility perceptions were nearly equal by cohort, with findings being essentially unchanged even when responses of “50%” were omitted from analysis (self-referred when “50%” is omitted: 42.4% vs systematically recruited: 43.3%, $t=-.4$, $p=.73$). The self-referred cohort and systematically recruited cohorts were also nearly identical on testing beliefs, with both cohorts scoring benefits far greater than risks and limitations. AD causal beliefs did not differ by cohort, either. The importance of genetics or heredity in increasing one’s risk for AD was rated .66 points higher on 5-point scales than lifestyle among self-referred participants ($t=10.5$, $p<.001$) and .58 points higher among systematically recruited participants ($t=5.56$, $p<.001$). Coping self-efficacy was nearly identical between cohorts, with approximately half of each cohort rating their

likelihood of coping with results indicating increased AD risk over 90%. Finally, AD control was nearly identical among both cohorts, averaging 3.1 and 3.2 on 5-point scales for both cohorts in the second and third trials, respectively. Findings did not change when adjusting for differences in baseline demographics.

Given the potential for differences on psychosocial factors to be introduced through differentials in study attrition by demographic factors, I examined measures administered in the mailed questionnaire by race. Individuals who self-identified as black or African American rated, on average, both the benefits of testing and the risks and limitations higher than other racial groups (benefits mean: 3.77 vs 3.48, $t=3.81$, $p<.001$; risks and limitations mean: 2.08 vs 1.85, $t=3.32$, $p<.001$). African Americans had lower AD worry than other racial groups (1.79 vs 2.12, $t=-3.99$, $p<.001$) and lower AD concern (3.32 vs 3.51, $t=-2.46$, $p=.014$). No other differences by race were evident on psychosocial constructs. Similarly, I also examined psychosocial measures administered during the phone interview and in the mailed questionnaire by study site. Individuals enrolled at Howard University rated both the benefits and the risks and limitations of testing higher than individuals at other sites (benefits mean: 3.74 vs 3.48, $t=3.47$, $p<.001$; risks and limitations mean: 2.13 vs 1.83, $t=4.43$, $p<.001$). No differences by site were evident on hereditary/genetics causal beliefs, but participants at Case Western Reserve rated the importance of lifestyle for AD risk higher than participants at other sites (mean: 3.69 vs 3.38, $t=2.89$, $p=.004$). Participants at Howard University reported lower AD worry on average than participants at other sites (mean: 1.84 vs 2.11, $t=-3.28$, $p<.001$). No differences were evident on AD control.

DISCUSSION

This is one of the first analyses to explore how study referral processes affect the profile of participants in genetic susceptibility testing research. Both self-referred and systematically recruited participants tended to be well-educated and have high household incomes. In addition, over 90% of participants overall expressed interest in genetic susceptibility testing for AD, a level even higher than typically found in studies of hypothetical genetic susceptibility testing for AD, where 35% to 75% of participants express interest in testing (Binetti et al., 2006; Moscarillo et al., 2007; Neumann et al., 2001). Participants in the REVEAL Study were clearly unrepresentative of the general public, whether they were self-referred or systematically recruited.

Nevertheless, analyses supported a number of hypotheses about demographic differences by referral process. The self-referred cohort was younger and more educated than the systematically recruited cohort, as noted in the first REVEAL Study trial (Roberts et al., 2004). Also, household incomes were higher and family histories of AD stronger among the self-referred cohort, at least at intake. Contrary to findings from the first trial – but hypothesized correctly here – self-referred participants were less likely to self-report African American ethnicity. In fact, substantially lower ethnic diversity among the self-referred cohort is one of the most notable findings from these analyses, as the systematically recruited cohort had more than double the percentage of African Americans at intake. Prior research has found African Americans to have less interest in hypothetical testing for AD (Hipps, Roberts, Farrer, & Green, 2003) and actual testing for genetic susceptibility to other diseases (Alford et al., 2011). The same study and one other found African Americans to perceive fewer benefits and more risks and limitations

relative to Caucasians (Hippis et al., 2003; Peters, Rose, & Armstrong, 2004), contrary to what was found in these analyses. These apparent inconsistencies might be explained by racial differences in attitudes about research, medicine and AD. African Americans often have greater mistrust in researchers and the medical system (Furr, 2002; Singer, Antonucci, & Van Hoewyk, 2004; Thompson, Valdimarsdottir, Jandorf, & Redd, 2003). In addition, African Americans may have more favorable attitudes towards caregiving and less interest about AD relative to other medical concerns (Gallagher-Thompson et al., 2000) and therefore feel less motivated to pursue screening to resolve uncertainty or facilitate prevention. It is possible that African Americans who actually enroll in the REVEAL Study perceive greater benefits to testing than other racial groups because they would otherwise avoid testing due to lower interest in AD in general or mistrust of the medical system or research. Researchers need to be sensitive to the possibility that psychosocial factors driving uptake of genetic susceptibility testing among Caucasians may be very different than psychosocial factors driving uptake among African Americans.

Predictions about education were not supported, despite findings from the first REVEAL Study trial. It is possible that education, although associated with participation in research more generally, has a more complicated association with attitudes about genetic susceptibility testing. Education did not predict information seeking or uptake of testing in the Multiplex Initiative (Alford et al., 2011), and a recent national survey found greater education to be associated with *lower* hypothetical uptake of testing for AD (Neumann et al., 2012). The systematically recruited cohort in the analyses for this paper was also comprised largely of individuals who had participated in other studies, and

participation in clinical trials is often skewed towards individuals with more education (Baquet, Commiskey, Daniel Mullins, & Mishra, 2006; Sateren et al., 2002). The null finding on education might be because systematic recruitment in the REVEAL Study drew from a population that was well-educated to begin with, whereas self-referral attracted highly-educated individuals from a more diverse pool.

Differences on gender also failed to achieve statistical significance overall, but interpretation of this null finding is complicated by the gender quota instituted in the third trial. Recruitment efforts did not target specific genders or age groups, but systematic recruitment started early and stopped as enrollment targets were neared. What this means is that individuals who wanted to enroll but could not because a specific demographic target was satisfied were more likely to be self-referred. As mentioned earlier, gender differences by referral cohort were evident in the first and second trials where gender quotas did not exist. Also, at the Michigan site in the third trial, 84% of waitlisted individuals were female, and nearly all had self-referred to the study after reading about it in the newspaper. Numerous reasons exist why women would be more interested in genetic susceptibility testing for AD than men. Women are at increased risk for AD (Green et al., 2002). In addition, women generally take more responsibility for the nutrition, health, and hygiene of their families (Lane & Cibula, 2000), including the caregiving role for AD patients (Alzheimer's Association, 2011); and women more often coordinate care with physicians and genetics clinics on behalf of other family members (Koehly et al., 2003; Stacey, 1996). Had gender quotas not existed in the third REVEAL Study trial, it is probable that women would have constituted a much larger percentage of the self-referred cohort than shown in these analyses.

Data supported hypotheses about interest in testing, at least at the point of enrollment. Self-referred participants were more likely to express definitive interest in genetic testing than systematically recruited participants, although the difference did not exist among the subset of participants who retained in the study through completion of the mailed questionnaire. Notably, almost two thirds of individuals who were not interested or maybe-interested in genetic susceptibility testing for AD dropped out of the study before completing the mailed questionnaire and before the education stage of the study. Data also supported hypotheses about differences by referral cohort on baseline emotional factors. Bivariate analyses showed greater worry and concern about AD among the self-referred cohort at intake, but differences on concern were borderline when controlling for demographic factors.

Analyses did not support hypotheses about differences on other cognitive factors. Both cohorts rated the benefits far greater than they rated the risks and limitations, and both cohorts rated the contribution of genetics to AD risk as greater than the contribution of lifestyle. Participants in both cohorts tended to overestimate their susceptibility for AD, had strong confidence in their ability to cope with results, and tended to neither agree nor disagree that AD was controllable. A criticism of research on genetic susceptibility testing has been its reliance on self-selected samples (McBride et al., 2010). While systematic recruitment can improve the ability of researchers to assess the external validity of research findings, the sample it enrolls is still one that is self-selected and may be strongly favorable towards genetic susceptibility testing. Further work will need to examine whether the disparities observed in this study of AD susceptibility testing are evident in other testing contexts and for other diseases.

Differential dropout complicates some analyses in this paper. African Americans and Howard University participants were more likely to drop out before completing the mailed questionnaire, on which these groups both rated the benefits and the risks and limitations of testing higher in bivariate analyses than their counterparts. Furthermore, participants from Case Western Reserve, who had stronger lifestyle causal beliefs, were more likely to drop out than participants from other sites within the self-referred cohort. The potential exists that differences by cohort existed at intake on testing beliefs and causal beliefs, but were no longer evident when constructs were measured due to the aforementioned differences in study attrition. The similarities in values reported by the retained sample, though, suggest that differences would be small if they existed at all.

For practitioners, the findings from these analyses provide insight about the kinds of populations that may seek AD genetic susceptibility testing offered in clinical or consumer settings. Proposals about whether or not to communicate information of questionable utility to patients, particularly results derived through whole genome sequencing, include allowing patients to decide (Berg, Khoury, & Evans, 2011; Institute of Medicine, 2012). Whether such information would be proffered by physicians to individuals or whether individuals would have to proactively request the information has yet to be decided. Furthermore, direct-to-consumer genetic test providers like 23andMe have recently introduced *APOE* testing for AD risk into their panels, and while marketing to date has relied primarily upon self-referral, strategies may be adopted in the future that target specific individuals based on associations. These analyses in this paper provide insight about who may express interest in testing and how the profile of test seekers may change depending on what kind of recruitment or marketing strategies are used.

For researchers, the analyses presented here highlight the challenge of generalizing findings from existing research. Self-referral yielded a cohort that was not equivalent to the sample enrolled through systematic recruitment. High-profile studies of genetic susceptibility testing, such as the Scripps Genomic Health Initiative (Bloss et al., 2010) and the Coriell Personalized Medicine Collaborative (Gordon et al., 2010), have largely collected data from self-referred samples. Admittedly, the REVEAL Study focuses on single-gene testing to determine risk for a single disease with no proven prevention options whereas those other studies focus on multi-gene testing to determine risk for multiple modifiable conditions. How well the REVEAL Study represents the current generation of genetic susceptibility tests is therefore debatable. It seems likely, though, that the differences in study populations observed in the REVEAL Study would exist for other studies of susceptibility testing.

Findings also have implications about the kinds of theories that might be used as the foundation of genetic susceptibility testing research. Much research on genetic susceptibility testing has been predicated on popular health behavior theories like the Health Belief Model (Rosenstock, 1974) and the Theory of Planned Behavior (Ajzen, 1991), theories that emphasize the role of cognitions in decisions about services and preventive behaviors. If referral process has an important impact on test uptake and post-disclosure health behavior change, then the psychosocial factors mediating that relationship aren't likely to be cognitive factors like beliefs about the benefits of testing or the controllability of AD, but instead may be about emotional factors like concern and worry. While great attention has been devoted to the impact of testing on emotional wellbeing, far less research on genetic susceptibility testing has examined the role of

emotions in decision-making about test uptake or post-disclosure health behavior changes. These omissions occur despite consistent evidence that responses to risk information are as contingent on emotional factors as cognitive responses (Schwartz et al., 2003; Zikmund-Fisher, Fagerlin, & Ubel, 2010). The importance of emotion in decision making is further supported by a growing body of neurobiological and neuroimaging evidence that shows that emotions affect decisions through processes that are distinct from cognitive reasoning (Arnsten, 1998; Bechara, Damasio, Tranel, & Damasio, 1997). The analyses here suggest that theories that recognize the role of emotion in decision making and behavior merit more attention in genetic susceptibility testing research, particularly because individuals who are emotionally invested in an event often selectively process information in ways that are consistent with existing goals (Kunda, 1990; Liberman & Chaiken, 1992).

Limitations

Some important limitations must be noted with respect to these analyses. First and foremost, inattention to certain processes of recruitment, such as a failure to track how many recruitment mailings were sent or how many families were approached in the waiting areas of neurology clinics, mean that response rates cannot be calculated. Second, the analyses in this paper compare self-referral strategies against systematic recruitment with a focus on process, but differences in sampling frames may have just as important an effect. While recruitment efforts facilitating self-referral often targeted broad audiences, systematic recruitment tended to target populations with connections to AD treatment or research, such as families seen in neurology clinics or members of AD research registries. The analyses presented here are unable to tease apart what is a function of the targeted

universe and what was a function of process. The optimal study of referral process would ensure that sampling frames were as equivalent as possible (e.g., mailings to subscribers of a dementia newsletter versus study advertising in the newsletter itself).

Lastly, comparisons to other studies on referral processes ignore the motivations for referral. In situations like risk assessments for heart disease or binge eating interventions, clear behavioral responses exist that would reduce disease risk. In contrast, genetic susceptibility testing for AD is missing a behavioral outcome that would qualify as optimal. For interventions to improve health outcomes, differences between systematically recruited cohorts and cohorts who self-refer may be stronger because behaviors exist which participants *should* do but may not want to do. The desire to be a “good patient” and satisfy expectations of referring physicians may motivate individuals who are systematically recruited for a diet intervention to participate, despite a lack of intrinsic motivation for improved health or weight loss (Schwarz, 1994). Opinion leaders often discourage genetic susceptibility testing for AD, in contrast, and the extrinsic pressure individuals may feel about following through with a behavior like test uptake is likely to be far weaker for REVEAL Study participants. Consequently, both self-referred and systematically recruited participants in the REVEAL Study are likely to have strong intrinsic motivation for testing.

Conclusions

Results from these analyses confirm that self-referral to genetic susceptibility testing research enrolls participants that differ from participants enrolled through systematic recruitment on important demographic factors. It also enrolls individuals who are more interested and slightly more concerned and worried about AD, but are otherwise

comparable to systematically recruited participants. Future papers will examine how these differences affect test uptake as well as responses to AD risk assessment with genotype disclosure.

TABLES

Table 2. Psychosocial constructs found to be associated with greater likelihood of undergoing actual or hypothetical testing.

| Construct and Association | Condition/Test | Reference |
|---|--|--|
| Greater interest in testing | HBOC, lung cancer | Lerman et al., 1997; Sanderson, O'Neill, Bastian, Bepler, & McBride, 2009 |
| Perceiving more benefits of testing | HBOC, melanoma, unspecified cancer, bipolar disorder | Bosompra et al., 2000; Kasparian, Meiser, Butow, Simpson, & Mann, 2009; Lerman et al., 1996; Meiser et al., 2008 |
| Perceiving fewer risks and limitations of testing | AD, melanoma, hereditary breast and ovarian cancer | Christensen, Roberts, Uhlmann, & Green, 2011; Kasparian et al., 2009; Lerman et al., 1996 |
| Greater perceived disease susceptibility | Melanoma | Kasparian et al., 2009 |
| Perceiving disease as less severe | Multiplex testing | McBride et al., 2009 |
| Greater disease controllability | Various compared | Marteau & Croyle, 1998 |
| Stronger genetic causal beliefs | Unspecified cancer | Henrikson et al., 2007 |
| Perceiving more health behaviors in need of improvement | Multiplex testing | McBride et al., 2009 |
| Greater self-efficacy about understanding genetics | Multiplex testing | McBride et al., 2009 |
| Greater worry | AD | Roberts et al., 2004 |

Table 3. How participants learned about the REVEAL Study by trial.

| | Second Trial (n=437) | Third Trial (n=380) | Total (n=817) | % of Cohort |
|--------------------------------------|----------------------------|---------------------------|------------------|----------------|
| <i>Systematically recruited</i> | 160 | 89 | 249 | 100.0% |
| From another research study | 84 | 65 | 149 | 59.8% |
| Called at home or work | 33 | 2 | 35 | 14.1% |
| Provider referral | 10 | 15 | 25 | 10.0% |
| Mailing | 9 | 6 | 15 | 6.0% |
| Clinic intake | 12 | 0 | 12 | 4.8% |
| Alzheimer's Disease Center referral | 7 | 0 | 7 | 2.8% |
| Talked to in waiting room | 5 | 1 | 6 | 2.4% |
| <i>Self-referred</i> | 263 | 283 | 546 | 100.0% |
| Brochure or advertisement | 89 | 144 | 233 | 42.7% |
| Media | 27 | 64 | 91 | 16.7% |
| Web site | 33 | 31 | 64 | 11.7% |
| Presentation | 35 | 14 | 49 | 9.0% |
| From a friend | 31 | 18 | 49 | 9.0% |
| Heard from family/friend/participant | 27 | 10 | 37 | 6.8% |
| Health fair | 9 | 1 | 10 | 1.8% |
| Wait list from prior trial | 10 | 0 | 10 | 1.8% |
| “Self-referred” | 2 | 1 | 3 | 0.5% |
| <i>Unknown</i> | 14 | 8 | 22 | 100.0% |

Table 4. Descriptive statistics of REVEAL Study participants by referral cohort.

| | Systematically Recruited (n=249) | Self-Referred (n=546) | Total (n=795) | p |
|--|-------------------------------------|--------------------------|------------------|-----------------|
| <i>Continuous/ordinal variables: mean (sd)</i> | | | | |
| Age in years | 61.7 (12.0) | 56.2 (12.0) | 57.9 (12.2) | <.001 |
| Years of education* | 16.1 (3.0) | 16.3 (2.4) | 16.2 (2.6) | .177 |
| # of affected relatives | 1.6 (1.1) | 1.7 (1.2) | 1.7 (1.2) | .036 |
| Median income* | \$50-69K | \$70-99K | \$70-99K | .001 |
| <i>Categorical variables: n (%)</i> | | | | |
| Black/African American | 86 (34.7%) | 81 (14.9%) | 167 (21.1%) | <.001 |
| Male | 87 (34.9%) | 182 (33.3%) | 264 (33.8%) | .671 |
| Employed part/full time* | 99 (50.5%) | 323 (66.9%) | 422 (62.2%) | <.001 |
| ε4 carrier† | 46 (33.6%) | 144 (37.1%) | 190 (36.2%) | .459 |
| Site by referral cohort | | | | <.001 |
| Boston University | 122 (49.0%) | 126 (23.1%) | 248 (31.2%) | |
| Case Western Reserve | 46 (18.5%) | 145 (26.6%) | 191 (24.0%) | |
| Howard University | 63 (25.3%) | 115 (21.1%) | 178 (22.4%) | |
| Weill School of Medicine | 11 (4.4%) | 84 (15.4%) | 95 (11.9%) | |
| University of Michigan | 7 (2.8%) | 76 (13.9%) | 83 (10.4%) | |
| Trial by referral cohort | | | | <.001 |
| 2 nd Trial | 160 (64.3%) | 263 (48.2%) | 423 (53.2%) | |
| 3 rd Trial | 89 (35.7%) | 283 (51.8%) | 372 (46.8%) | |

* Assessed during the telephone interview (196 systematically recruited participants, 484 self-referred participants, 680 total)

† Determined through genotyping among participants who provided blood samples (137 systematically recruited participants, 388 self-referred participants, 525 total)

Table 5. Comparisons of participants who dropped out of the study before completion of the pre-education questionnaire against those who completed that step, stratified by referral cohort.

| | <i>Systematically Recruited</i> | | | <i>Self-Referred</i> | | | <i>Total</i> | | |
|--|---------------------------------|------------------|-------------|----------------------|------------------|-----------------|--------------|------------------|-----------------|
| | Lost (n=86) | Retained (n=163) | p | Lost (n=103) | Retained (n=443) | p | Lost (n=189) | Retained (n=606) | p |
| <i>Continuous/ordinal variables: mean (sd)</i> | | | | | | | | | |
| Age | 62.6 (12.0) | 61.3 (12) | .396 | 54.9 (13.2) | 56.5 (11.7) | .200 | 58.4 (13.3) | 57.8 (11.9) | .589 |
| Years of education* | 16.2 (3.5) | 16.1 (2.9) | .794 | 16.1 (2.5) | 16.3 (2.4) | .548 | 16.1 (3.0) | 16.2 (2.6) | .734 |
| # of affected relatives | 1.6 (1.1) | 1.6 (1.2) | .841 | 1.7 (1.1) | 1.8 (1.2) | .955 | 1.6 (1.1) | 1.7 (1.2) | .676 |
| Median income* | \$50-69K | \$50-69K | .894 | \$70-99K | \$70-99K | .471 | \$70-99K | \$70-99K | .374 |
| <i>Categorical variables: n (%)</i> | | | | | | | | | |
| Black/African American | 38 (44.7%) | 48 (29.4%) | .017 | 20 (19.6%) | 61 (13.8%) | .135 | 58 (31.0%) | 109 (18.0%) | <.001 |
| Male | 26 (30.2%) | 61 (37.4%) | .258 | 29 (28.2%) | 153 (34.5%) | .216 | 55 (29.1%) | 214 (35.3%) | .115 |
| Employed part/full time* | 17 (51.5%) | 82 (50.3%) | .899 | 30 (73.2%) | 293 (66.3%) | .371 | 47 (63.5%) | 375 (62.0%) | .798 |
| Site by referral cohort | | | .234 | | | <.001 | | | <.001 |
| Boston University | 44 (51.2%) | 78 (47.9%) | | 18 (17.5%) | 108 (24.4%) | | 62 (32.8%) | 186 (30.7%) | |
| Case Western Reserve | 11 (12.8%) | 35 (21.5%) | | 36 (35.0%) | 109 (24.6%) | | 47 (24.9%) | 144 (23.8%) | |
| Howard University | 27 (31.4%) | 36 (22.1%) | | 37 (35.9%) | 78 (17.6%) | | 64 (33.9%) | 114 (18.8%) | |
| Weill School of Med | 2 (2.3%) | 9 (5.5%) | | 5 (4.9%) | 79 (17.8%) | | 7 (3.7%) | 88 (14.5%) | |
| Univ of Michigan | 2 (2.3%) | 5 (3.1%) | | 7 (6.8%) | 69 (15.6%) | | 9 (4.8%) | 74 (12.2%) | |
| Trial by referral cohort | | | .298 | | | .724 | | | .282 |
| 2nd trial | 59 (68.6%) | 101 (62.0%) | | 48 (46.6%) | 215 (48.5%) | | 107 (56.6%) | 316 (52.1%) | |
| 3rd trial | 27 (31.4%) | 62 (38.0%) | | 55 (53.4%) | 228 (51.5%) | | 82 (43.4%) | 290 (47.9%) | |

* Assessed in telephone interview (systematically recruited participants lost = 33, self-referred participants lost = 41, total lost = 74)

Table 6. Summary of logistic regression model predicting study dropout before completion of baseline written questionnaire based on intake demographic variables (n=764).

| | OR (95% CI) | Z | p |
|---|-----------------|-------|-------------|
| Intercept | .41 (.14-1.19) | -1.63 | .103 |
| Age (per year) | 1.00 (.99-1.02) | .50 | .620 |
| # of affected relatives | .96 (.82-1.11) | -.53 | .597 |
| Black/African American (ref: any other race) | .87 (.51-1.46) | -.52 | .600 |
| Male (ref: female) | .85 (.58-1.24) | -.84 | .402 |
| Site (ref: Boston University) | 1.15 (.73-1.82) | .61 | .541 |
| Case Western Reserve | 1.64 (.95-2.83) | 1.78 | .075 |
| Howard University | .29 (.11-.64) | -2.83 | .005 |
| Weill School of Medicine | .50 (.21-1.05) | -1.74 | .083 |
| University of Michigan | .94 (.65-1.38) | -.30 | .763 |
| 3rd trial (ref: 2nd trial) | .56 (.38-.83) | -2.90 | .004 |
| Self-referred (ref: systematically recruited) | .85 (.58-1.24) | -.84 | .402 |

Overall model evaluation

Likelihood ratio test: $\chi^2=42.4$, df=10, p<.001

Goodness of fit

Hosmer & Lemmestow test: $\chi^2=13.0$, df=8, p=.111

Table 7. Unadjusted bivariate associations between key psychosocial factors and referral processes for (A) the total sample at each measurement point and (B) the sample that completed the mailed questionnaire. Figures represent means and standard deviations, except where noted.

| | | <i>Total Sample (n varies by measure)</i> | | | | <i>Retained Sample</i> | | | |
|---|-----------------------------------|---|-------------------|----------------|-----------------|-------------------------------|------------------------------|------------------|-----------------|
| | | System. Recruit | Self- Referred | Total | p | System. Recruit (n=163) | Self- Referred (n=443) | Total (n=606) | p |
| <i>Measured at intake n=795 (249 sys, 546 s-r)</i> | Interested in genetic test: n (%) | 220 (89.1%) | 522 (95.6%) | 742 (93.6%) | <.001 | 156 (95.7%) | 431 (97.3%) | 587 (96.9%) | .160 |
| | Perceived susceptibility | 45.3% (1.6%) | 45.0% (1.1%) | 45.1% (.9%) | .564 | 46.1% (2.0%) | 45.6% (1.2%) | 45.7% (1.0%) | .596 |
| | Perceived seriousness | 3.11 (.09) | 3.17 (.06) | 3.15 (.05) | .710 | 3.13 (.11) | 3.20 (.07) | 3.18 (.06) | .714 |
| | AD concern | 3.34 (.05) | 3.47 (.03) | 3.43 (.03) | .016 | 3.40 (.06) | 3.50 (.03) | 3.47 (.03) | .065 |
| <i>Measured in phone interview n=680 (196 sys, 484 s-r)</i> | AD worry | 1.87 (.06) | 2.12 (.04) | 2.04 (.03) | <.001 | 1.87 (.06) | 2.13 (.04) | 2.06 (.03) | <.001 |
| | Coping self-efficacy | 86.1% (1.3%) | 85.7% (.8%) | 85.8% (.7%) | .595 | 86.1% (1.4%) | 86.1% (.9%) | 86.1% (.7%) | .498 |
| <i>Measured in mailed questionnaire</i> | Perceived benefits | | | | | 3.55 (.06) | 3.53 (.03) | 3.53 (.03) | .634 |
| | Perceived risks and limitations | | | | | 1.94 (.05) | 1.87 (.03) | 1.89 (0.03) | .161 |
| | Hereditary/genetics causal belief | | | | | 4.03 (.07) | 4.11 (.04) | 4.09 (.03) | .141 |
| | Lifestyle causal belief | | | | | 3.45 (.09) | 3.45 (.05) | 3.45 (.05) | .510 |
| | AD control | | | | | .03 (.08) | -.02 (.05) | -.01 (.04) | .706 |

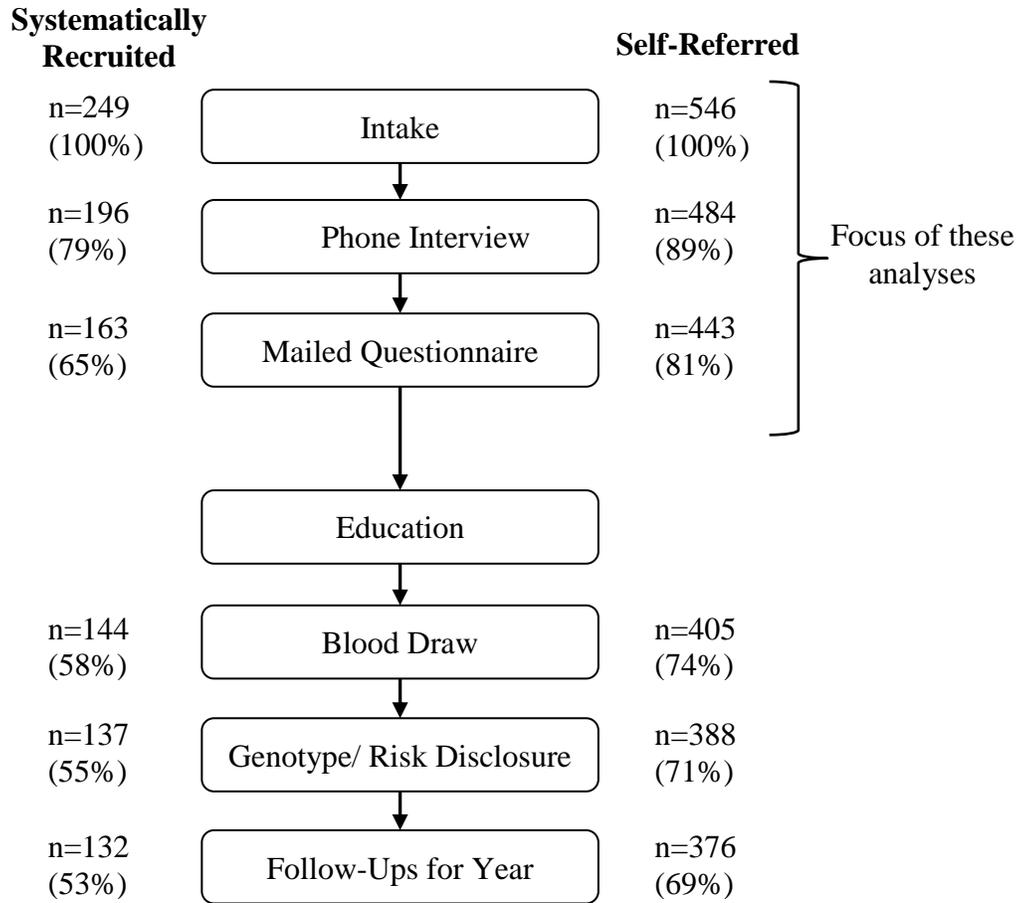
sys = systematically recruited cohort, *s-r* = self-referred cohort

Table 8. Differences on key psychosocial factors for self-referred participants compared to systematically recruited participants, adjusting for age, race, income, employment status, study site, and study trial: sample retained through completion of the pre-education questionnaire (n=606).

| Factor | Δ | Std error | t | P |
|-----------------------------------|----------|-----------|-------|-------------|
| Perceived susceptibility | 3.74 | 2.19 | 1.71 | .044 |
| Perceived seriousness | .13 | .14 | .92 | .180 |
| AD concern | .10 | .07 | 1.39 | .083 |
| AD worry | .20 | .08 | 2.63 | .004 |
| Perceived benefits | .00 | .07 | .04 | .484 |
| Perceived risks and limitations | -.07 | .07 | -1.13 | .129 |
| Hereditary/genetics causal belief | -.02 | .08 | -.26 | .603 |
| Lifestyle causal belief | -.07 | .11 | -.61 | .728 |
| Coping self-efficacy | -.41 | 1.82 | -.23 | .590 |
| AD control | -.07 | .10 | -.74 | .769 |

FIGURES

Figure 3. REVEAL Study flow chart, with sample size at each step by referral process.



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CHAPTER 5

ASSOCIATIONS WITH PRETEST EDUCATION AND TEST UPTAKE

BACKGROUND

Genetic susceptibility testing for Alzheimer’s disease (AD) is increasingly available in both clinical and consumer settings. In the 1990s, numerous professional organizations and working groups issued consensus statements strongly discouraging genetic testing of asymptomatic individuals for AD risk due to limitations in its predictive value and a lack of proven prevention options (Brodaty et al., 1995; McConnell, Koenig, Greely, & Raffin, 1999; NIA/Alzheimer's Association Working Group, 1996). The American College of Medical Genetics (ACMG) and the National Society of Genetic Counselors (NSGC) have recently softened their stances, though, asserting that “testing may be considered at the clinician’s discretion” (Goldman et al., 2011, p. 601). Furthermore, direct to consumer (DTC) genetic testing companies like 23andMe and deCODE recently incorporated markers for AD into their panels. These developments highlight a need to understand factors that affect who seeks information about testing, how those people respond to pre-test education, and who ultimately undergoes testing.

One important factor may be whether or not individuals self-refer to testing. Self-referral can be defined as situations where individuals learn about genetic susceptibility testing through newspaper advertising, word-of-mouth, or information on the Internet and then proactively contact a test provider. This way of obtaining testing stands in contrast to systematic recruitment where individuals react to targeted offers, such as when physicians refer individuals to testing or when providers send targeted mailings or make phone calls to individuals with an offer of services. Self-referral to testing, whether in clinical research settings or through DTC services, likely attracts individuals with greater intrinsic motivation for testing given how it requires them to initiate contact with providers, whereas systematic recruitment simply requires individuals to respond to testing offers.

These differences in motivation have the potential to affect how information provided before testing changes cognitions about disease, testing, and behaviors. Although genetic testing protocols vary from situation to situation and provider to provider, nearly all protocols involve some type of pretest education to address potential misunderstandings. Americans frequently overestimate the capabilities of genetic services, believing that tests for qualities such as intelligence and technologies such as gene therapy are currently being used (Genetics and Public Policy Center, 2004; Singer, Corning, & Lamias, 1998); and those who seek genetic services often score little better than random chance on genetic knowledge assessments (Scheuner, Sieverding, & Shekelle, 2008; Walter, Emery, Braithwaite, & Marteau, 2004). Pretest education is important to ensure test recipients have realistic expectations about what testing entails and what it can accomplish. The aforementioned practice guideline issued jointly by

ACMG and NSGC emphasize that pretest education for AD susceptibility testing should highlight the following points:

- Proven pharmacologic or lifestyle interventions to reduce AD risk or stop AD progression are lacking
- The general population risk is between 10-12% in a 75-80 year lifespan
- How ethnicity affects risk is not well known
- Genes likely exist that are associated with AD but have not yet been identified
- *APOE* testing does not give definitive information about future AD onset or avoidance
- Results can potentially impact insurability, although state and federal legislation provides some protection (Goldman et al., 2011)

While education that covers these points is sure to correct some misperceptions, its effectiveness may be stronger among individuals who self-refer to testing than among systematically recruited individuals. A popular communication theory, the Elaboration Likelihood Model (ELM), asserts that the persuasiveness of a health communication is contingent upon a person's motivation to process it and ability to understand it (Petty, Barden, & Wheeler, 2002). It is likely that individuals who self-refer to AD genetic susceptibility testing have greater motivation to be tested compared to individuals who are systematically recruited, at least at the point of initiating contact with the test provider. In addition, the potential exists that self-referred individuals have greater knowledge of AD and genetic susceptibility testing than systematically recruited individuals. If either scenario is correct, pretest education might be more effective for

participants who self-refer to testing than for individuals who are systematically recruited.

One way to gain insight about this issue is to examine cohorts enrolled in the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study. Since 1999, the REVEAL Study has examined how asymptomatic individuals seek and respond to genetic susceptibility testing for AD using apolipoprotein E (*APOE*), whose $\epsilon 4$ allele is a robust risk factor for AD. The REVEAL Study has used a variety of processes to recruit participants, including advertising through flyers, newspapers, and Internet postings which encourage self-referral. It has also systematically recruited participants through targeted mailings, calls to participants of research registries, and referrals from other clinicians and researchers. If self-referral favors individuals who are more motivated and able to receive genetic risk information than systematic recruitment, then the self-referred cohort in the REVEAL Study sample may show greater changes to cognitions about AD following pre-test education than the systematically recruited cohort.

The REVEAL Study assessed few psychosocial constructs in a way that distinguishes the impact of pretest education from the impact of genetic risk disclosure. One important construct that *was* assessed both before and after education, but before disclosure of testing results, was AD susceptibility perceptions. Analyses in the prior dissertation paper showed both self-referred and systematically-recruited individuals reported their AD risk at intake as 45% on average, well above risks quoted in educational materials of between 10% and 15%. If self-referred participants are more motivated to or capable of processing pretest educational information than systematically recruited participants, then we would expect the AD susceptibility perceptions to change

more often among self-referred participants than systematically recruited participants. The analyses conducted here test that supposition.

Hypothesis 1: Self-referred participants in the REVEAL Study are more likely to report changes to AD susceptibility perceptions than systematically recruited participants after pretest education.

These potential differences in how education changes cognitions, in conjunction with initial differences in overall motivation, may translate into a second important and understudied area: the likelihood that individuals actually follow through with testing. Genetic susceptibility testing for AD arguably has little to no clinical utility, and a reasonable and often-recommended decision about AD susceptibility testing is to forego it altogether. Data from the first REVEAL Study trial suggested that self-referred participants were more likely to ultimately have *APOE* genotyping and receive AD risk estimates compared to systematically recruited participants (Roberts et al., 2004). However, these analyses did not attempt to differentiate general study attrition from the specific impact of pretest education. Disparities may have occurred primarily during the initial phases of the first REVEAL trial, which were devoted to data collection and deliberately omitted information about the process and capabilities of testing to minimize “contaminating” data about the efficacy of education. Analyses in the prior dissertation paper show that self-referred participants in the second and third trials were more likely to be retained through the earliest steps of the study, even after controlling for demographic differences. While individuals who drop out of the study before pretest education are likely to have lower motivation for testing than individuals who remained

in the study, it is probable that early dropout was unassociated with anything learned about *APOE* testing.

Disparities in uptake rates between self-referred and systematically recruited individuals may result from differences at enrollment on key psychosocial factors. A version of the conceptual model underpinning this dissertation, focusing on analyses to be conducted in this paper, is presented in Figure 4. Based on the Health Belief Model (Rosenstock, 1974), the model asserts that the likelihood of following through with testing is greater when individuals perceive more benefits and fewer risks and limitations to testing. It is also greater when individuals perceive themselves to be more susceptible to disease, when the disease is perceived to be more serious, and in recent iterations of the Health Belief Model (Rosenstock, Strecher, & Becker, 1988), when self-efficacy about testing is high. The model also draws from the Common Sense Model of Self Regulation (CSM), and posits that testing might occur as a coping response to distress about disease, assuming that individuals' perceptions about AD align with testing (Gooding, Organista, Burack, & Biesecker, 2006; Leventhal, Leventhal, & Contrada, 1998). The prior paper showed that self-referred REVEAL Study participants had greater levels of worry and concern about AD. The CSM would suggest, then, they would be more likely to follow through with testing.

Support for the core of the conceptual model can be found in work on actual and hypothetical susceptibility testing. Perceiving more benefits (Roberts et al., 2003) and fewer risks and limitations to AD genetic susceptibility testing (Christensen, Roberts, Uhlmann, & Green, 2011; Roberts et al., 2003) is correlated with higher rates of uptake in some REVEAL Study analyses. Illness perceptions are also often associated with

interest and intentions to undergo genetic susceptibility testing for other conditions, including greater personal susceptibility to illness (Bosompra et al., 2000; Bunn, Bosompra, Ashikaga, Flynn, & Worden, 2002), lower perceived severity of disease (McBride, Koehly, Sanderson, & Kaphingst, 2010), stronger beliefs that genetics contributes to disease risk (Henrikson, Harris, & Bowen, 2007), stronger beliefs that lifestyle changes can reduce disease risk (Marteau & Croyle, 1998), and stronger beliefs that the disease is controllable (Gooding et al., 2006). Behavioral beliefs, including greater self-efficacy about testing (Manne et al., 2007; McBride et al., 2009); and emotions such as greater worry and concern about illness (Cameron & Reeve, 2006) are other factors that may be associated with a greater likelihood of following through with testing. In short, testing beliefs, illness perceptions, behavioral beliefs, and emotional factors may all be important predictors of AD susceptibility testing uptake.

Analyses in the first paper of this dissertation found evidence of few referral group differences on these constructs. Self-referred participants had greater baseline interest and marginally greater AD concern than systematically recruited participants, but differences were no longer statistically significant among the population of study participants who remained in the study until they were offered pretest education. Only differences on AD worry persisted through the offer of pretest education. To the extent that psychological factors existing before education drive test uptake, limited reasons exist to expect disparities in test uptake to be evident. Nevertheless, examining the relationship of these factors with test uptake will provide insight about the validity of the conceptual model underpinning this dissertation.

Moreover, while few differences on psychosocial factors were evident prior to testing, there were significant differences on important demographic factors that may have an independent effect on test uptake. The previous paper found that self-referred participants were younger, had stronger family histories of AD, had higher household incomes, were more likely to be employed, and were less likely to self-identify as black or African American. These demographic differences may affect the uptake of testing in competing ways. In the studies of genetic susceptibility testing showing an effect of age on testing interest or uptake, greater interest often existed among older individuals for adult-onset conditions like breast cancer (Bloss et al., 2010; Donovan & Tucker, 2000; Kessler et al., 2005), suggesting that test uptake may be higher in systematically recruited participants. On the other hand, higher household income has been shown to be associated with fewer perceived negative outcomes for breast and ovarian cancer susceptibility testing (Donovan & Tucker, 2000); and most studies of genetic testing have found uptake of testing to be lower among African Americans relative to Caucasians (Alford et al., 2011; McQuillan, Porter, Agelli, & Kington, 2003).

Despite these complicated considerations, analyses in the prior paper showed less study dropout prior to pretest education among self-referred participants, even after controlling for differences on demographics. This finding serves as the basis for Hypothesis 2:

Hypothesis 2: Self-referred participants are less likely to drop out of the REVEAL Study prior to genetic risk disclosure than systematically recruited participants.

To test both hypotheses, I first summarized the profile of participants who were offered pre-test education, focusing on demographic and psychosocial factors potentially important to test uptake. I then explored baseline knowledge about AD and genetic testing before A) examining the impact of pretest education on knowledge scores to confirm its efficacy, and B) testing whether its ability to change susceptibility perceptions varied by referral cohort. Next, I examined factors that potentially mediate the relationship between referral status and test uptake. I tested whether self-referral has an independent effect on test uptake before finally comparing referral cohorts on their reasons for dropout.

METHODS

Overview

This chapter summarizes a secondary analysis of data from the second and third trials of the REVEAL Study, a series of multicenter randomized clinical trials examining the psychosocial and behavioral impact of providing AD susceptibility testing with *APOE* genotype disclosure (see Roberts (2011) for a summary of findings). The first REVEAL Study trial (1999-2003) compared the impact of a genetic risk assessment for AD against a risk assessment for AD based on non-genetic factors (i.e., family history and gender), but is excluded from these analyses because of inconsistencies about what constructs were assessed and how they were operationalized, relative to the other trials. The second trial (2003-2006) built on work from the first by expanding the participant profile to include more African Americans and by testing a condensed educational and counseling protocol against a traditional model based on genetic testing for cancer susceptibility. The third trial (2006-2009) explored the impact of disclosing that the $\epsilon 4$

allele of *APOE* is associated with coronary artery disease in addition to AD, and also tested a telephone disclosure protocol against in-person disclosure. In each trial, study sites decided individually how to recruit participants. Preliminary analyses of the primary study aims of the second and third trials have been presented elsewhere (Christensen, Roberts, Uhlmann, Whitehouse, Obisesan, Cupples, et al., 2010; Christensen, Roberts, Uhlmann, Whitehouse, Obisesan, Bhatt, et al., 2010; Green et al., 2006; Roberts et al., 2008) and are being reported separately.

Sites participating in the second trial included the Boston University School of Medicine in Boston, MA; Case Western Reserve Medical School in Cleveland, OH; the Weill School of Medicine in New York, NY; and the Howard University School of Medicine in Washington, DC. The third trial included the same sites, except the University of Michigan School of Public Health in Ann Arbor, MI replaced the Weill School of Medicine.

Procedures

Multidisciplinary teams of experts in the fields of AD, neurology, genetics, genetic counseling, health behavior, psychology, and bioethics created protocols in each trial. An External Advisory Board, as well as institutional review boards at each of the study sites, oversaw development and provided final approval. Figure 5 presents a study flow chart specifying when specific psychosocial factors were assessed. Following intake, participants provided informed consent for the parts of the study that preceded the blood draw for genotyping. Participants then completed a telephone interview followed by a self-administered mailed questionnaire. Upon return of the mailed questionnaire, participants received an offer of pretest education. In the second REVEAL Study trial,

where primary aims explored the effectiveness of different educational approaches, protocols randomized participants evenly into one of three arms. In an “extended” arm, education occurred during an in-person group educational session using PowerPoint slides and conducted by a genetic counselor (GC). Topics covered included: 1) a formal definition of AD; 2) general risk factors for AD (e.g., age, family history) and the general population’s level of risk; 3) *APOE* and its implications for risk of AD; 4) procedures involved in *APOE* testing; 5) a preview of what would be provided in their risk assessment (e.g., risk figures and their format, comparison groups); and 6) known benefits, risks, and limitations of *APOE* testing (e.g., lack of precision in risk estimates, potential privacy concerns regarding genetic information). Participants then reviewed their family history of dementia and personal medical information with a genetic counselor during a separate “blood draw” session, followed by a genetic counselor-directed discussion where counselors proactively addressed psychosocial aspects of testing such as the personal meaning of testing for participants. After establishing that they were still comfortable with a genetic risk assessment for AD, participants underwent a second informed consent step covering the second half of the study, including genetic testing for AD risk, and then provided blood for *APOE* genotyping at a CLIA-certified laboratory. The extended educational protocol was modeled after educational processes recommended for genetic susceptibility testing for cancer (Patenaude, 2004).

The second educational protocol in the second trial was a “condensed-GC” arm, which differed from the “extended” educational protocol on three key points. First, it replaced the in-person group education session with a mailed brochure summarizing the same key points as the PowerPoint presentation (Appendix 2 includes copies of

educational brochures). Second, rather than collecting family history and personal medical information in full during the blood draw session, participants provided this information on forms that were returned with the mailed questionnaire and reviewed by a genetic counselor prior to the blood draw session. Third, a participant-directed question-and-answer replaced the GC-directed discussion just prior to the blood draw. In all other respects, the condensed-GC protocol was the same as the extended protocol. The third educational protocol in the second trial was a “condensed-MD” arm which mirrored the condensed-GC arms in all respects, except a physician rather than a GC ultimately disclosed AD risk and *APOE* genotype information.

Based on preliminary analyses suggesting that the condensed protocols were as effective at conveying key educational points and posed no long-term psychological risks compared to the extended protocols (Green et al., 2007; Roberts, Chen, Uhlmann, & Green, In press), the condensed pretest education protocol was used for all participants in the third trial, with review of the family history and personal history information and question-and-answer sessions facilitated primarily by a genetic counselor.¹

Approximately one month after the blood draw, a GC or an MD (2nd trial only, “MD-condensed” arm) disclosed participants’ *APOE* genotypes and numerical risk assessments through age 85 ranging from 6% to 77% based on their *APOE* genotype, age, gender, self-identified ethnicity, and family history of AD. Details about how risk estimates were created are published elsewhere (Christensen et al., 2008; Cupples et al., 2004). Participants also received remaining AD risk estimates that incorporated current ages. All disclosures in the second trial occurred during in-person consultations. In the

¹ Near final stages of the third trial, a number of participants at the Howard University site met with a health educator rather than a genetic counselor.

third trial, participants were randomized to receive disclosure information in-person or via telephone, and randomized again to learn risk information about only AD or to learn about an association between *APOE* and coronary artery disease as well as AD risk information. REVEAL researchers then followed participants for the period of one year, with follow-ups occurring 1 week, 6 weeks, 6 months and 12 months after disclosure.

Given the focus of this paper on the association between self-referral and its impact on pretest education and test uptake, analyses presented here will use only data through the disclosure of risk information, focusing primarily on the period between the offer of pretest education and the uptake of testing.

Variables

Referral process

During intake, a research coordinator or research assistant queried participants about how they “heard about the REVEAL Study.” The coordinator or assistant then categorized verbal responses at the time of data collection into one of seven major response categories, described below. With help from the overall project managers of the second and third trials, I coded these classifications as systematically recruited or self-referred depending on who initiated contact. REVEAL Study personnel initiated contact with systematically recruited participants, whereas self-referred participants initiated contact with the REVEAL Study.

Coded as systematically recruited

1. *From another research study at this hospital (n=96).* Study personnel coordinated with researchers specializing in neurology and Alzheimer’s disease and encouraged them to discuss the REVEAL Study when appropriate. Examples include individuals

- who completed the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) examining the impact of anti-inflammatory medicines on AD risk (ADAPT Research Group, 2008); and individuals who agreed to donate their brains to AD research centers upon their death.
2. *Someone from the study talked to me in the waiting room (n=5).* Study personnel approached families in waiting areas of neurology and geriatrics clinics to explain the goals and steps of the research, and to attempt to enroll interested individuals.
 3. *Someone from the study called me at home or work (n=24).* Study personnel cold-called individuals whose provided telephone information for research purposes, usually as part of their participation in a research registry.

Coded as self-referred

4. *From a brochure or advertisement (n=177).* The research team created site-specific recruitment brochures and left them in locations where individuals with an interest in AD research might encounter them (e.g., the waiting rooms of neurology clinics). In addition, advertisements in local newspapers or posted flyers in strategic locations (e.g., clinics) provided information about the aims and methods of the study as well as a phone number and email address for interested individuals to use to initiate contact with REVEAL Study personnel.
5. *Someone from the study gave a presentation (n=41).* REVEAL Study personnel presented information about the study during community events about AD and AD research more generally. Study coordinators classified people who approached REVEAL Study personnel at the event and provided intake information or contacted the study afterwards in this category.

6. *From a friend (n=37)*. These individuals learned about the REVEAL Study from an acquaintance (e.g., a friend or co-worker) who was either a participant or had heard about the study another way, usually in the media (e.g., newspaper article, news report), and then initiated contact with a REVEAL Study coordinator.

Coded after further analysis

7. *Other*. At intake, the study coordinator or research assistant tagged individuals who didn't fit into the prior six categories as "other" and wrote descriptions. I recoded these descriptions into the following subcategories, after discussion with the project managers of the second and third REVEAL Study trials:

Coded as systematic recruitment

- a. *Alzheimer's Disease Center referral (n=4)*. These individuals contacted the Boston University Alzheimer's Disease Center and either wanted to participate in another study that was closed or for which they did not qualify; or accompanied an AD-affected relative to a research appointment for another study and were invited to participate. In both cases, participants did not have prior knowledge about the REVEAL Study.
- b. *Clinic intake (n=2)*. Howard University personnel classified individuals they approached at neurology clinics in this subcategory.
- c. *Provider referral (n=20)*. These individuals identified a specific nurse, physician, or genetic counselor who provided them information about the REVEAL Study.
- d. *Mailing (n=11)*. These individuals responded to a paper-based or electronic mailing sent to them because they had participated in ADAPT, because they

were members of the Michigan Alzheimer's Disease Research Center research registry, or because they were a member of the Dementia Coalition in Michigan.

Coded as self-referral

- e. *Heard from family/friend/participant (n=30)*. These individuals mentioned a specific individual (family member, friend, or a participant already in the study) who told them about the REVEAL Study.
- f. *Media (n=83)*. These individuals read about the REVEAL Study in a newsletter (e.g., Long Island Alzheimer's Foundation newsletter), newspaper article (e.g., *Ann Arbor News* press release), a book (e.g., *Carved in Sand*), or heard about it at an event (e.g., a Memory Walk) and found information about how to contact the REVEAL Study.
- g. *Self-referred (n=3)*. Study personnel tagged some individuals as "self-referred" without further elaboration.
- h. *Web site (n=55)*. These individuals either i) heard about the study in some unspecified manner and found a website created at one of the participating study sites; ii) visited a news or entertainment website that was discussing the REVEAL Study, such as *USA Today* online; iii) found REVEAL Study details on a website dedicated to helping studies enroll participants (e.g., *clinicaltrials.gov*, the University of Michigan ENGAGE website); or iv) said they had learned about the study "online," "on the internet," or through a "Google search" without being specific and initiated contact with study personnel.

- i. *Health fair (n=3)*. These individuals learned about the REVEAL Study by approaching a booth set up at a health fair by study personnel from Howard University.
- j. *Wait list from prior trial (n=10)*. Boston University waitlisted individuals who self-referred and wanted to participate in the first REVEAL Study trial but were excluded due to lack of space. Researchers invited them to participate in the second trial.

Primary Outcomes

Perceived AD susceptibility. Questionnaires assessed perceived AD susceptibility in the pre-education mailed questionnaire and in the post-education questionnaire using a single item that differed slightly by REVEAL Study trial. In the second trial, participants responded to the question, “on a scale of 0 to 100%, what do you think your chance of developing AD during your lifetime is?” In the third trial, participants responded to the question, “out of 100 people just like you, how many of them do you think will develop Alzheimer’s disease in their lifetime?”

Test uptake. For calculations using logistic regression, test uptake was coded ‘1’ if the participant remained in the study through the disclosure of AD risk and *APOE* genotype, ‘0’ otherwise.

Secondary Outcomes

Knowledge. Items from a scale developed for work on AD education (Moscarillo et al., 2007), and others created specifically for this study assessed knowledge about *APOE* and other risk factors for AD. Participants responded to four items administered both in the mailed questionnaire and in a post-education questionnaire (correct responses

are marked with an asterisk): 1) “What is the average person’s lifetime risk of getting AD?” (Greater than 75%/45-50%/*10-15%/1-5%); 2) “How are people’s chances of developing AD different if they have a parent or sibling who has had the disease?” (No difference/*Somewhat higher than other people in the general population/*A lot higher than other people in the general population)²; 3) “Can the APOE genetic test predict with certainty whether or not a person will get AD?” (*No/Yes/ Undecided); and 4) “How would you describe how having an APOE-4 gene affects the chances that someone will get Alzheimer’s disease?” (Makes it practically certain to not get AD/ Makes it somewhat less likely to get AD/ No effect on AD chances/*Makes it somewhat more likely to get AD/Makes it practically certain to get AD/Don’t know³). In addition, participants responded to five additional items administered only in the post-education questionnaire: 1) “Which of the following factors will be used to calculate your personal risk assessment?” (Your age/Your gender/Your APOE results/*All of the above) 2) “Men are more likely to develop Alzheimer's disease than women” (True/*False); 3) “In most cases, when do the first signs of Alzheimer's disease usually occur? (before age 60/*after age 60); 4) “A genetic test result that does not include a copy of the risk-increasing form of the APOE gene means that there is a 0% chance of developing AD” (True/*False); and 5) “Drugs are available to prevent Alzheimer's disease (True/*False). For analyses, responses were ultimately categorized as correct or not correct.

Item non-response on knowledge items was categorized as not correct (up to 15 instances per item in the pre-education questionnaire, up to 6 instances per item in the post-education questionnaire) except for two participants missing the post-education

² Both ‘somewhat higher’ and ‘a lot higher’ were deemed correct because the terms are subjective.

³ “Don’t know” was a response option in the mailed survey, but not in the post-education survey.

questionnaire altogether and for one participant missing an entire page from her post education questionnaire.

Reasons for dropout. A study coordinator asked participants who dropped out of the study for their reasons and classified responses into standardized response categories that varied by study trial. The second trial classified reasons for dropout in one of seven categories: a) concerns about emotional well-being; b) demands of study participation (e.g., too much time, travel); c) lack of prevention options for AD; d) concerns about privacy/confidentiality/ discrimination; e) limitations of test information; lack of interest; f) personal or family health problem; or g) other, with open-ended descriptions. The third trial classified reasons for dropout into the same categories along with three others: h) participant could not be reached to ascertain reason; i) no reason given; or j) deceased. For the purpose of combining data across trials, analyses combined ‘participant could not be reached’ and ‘no reason given’ with item non-response.

In addition to study dropout, participants were categorized as “screen outs” if they exceeded predetermined cutoffs for high anxiety, high depression, or low cognitive functioning on validated scales administered at the start of the blood draw appointment.

Demographics

Participants self-reported age, gender, race, and number of family members with AD at intake and confirmed that information during the phone interview or at the review of family history information provided just prior to blood draw. Racial groups were classified as “black/African American” and “other” in these analyses because individuals self-identifying as black or African American received one set of AD risk estimates and individuals self-identifying in any other racial category received a separate set of AD risk

estimates (note: individuals who self-identified as neither white/Caucasian nor black/African American were excluded from enrollment in the third trial at most sites. See the Participants and Recruitment section for an explanation). In addition, participants self-reported years of education, total household income (<\$10K, \$10-29K, \$30-49K, \$50-69K, \$70-\$99K, \$100K+, refuse to answer), and employment status (full-time, part-time, unemployed, or retired) during the telephone interview. Study records provided information about study site and trial round (second or third trial), as well as *APOE* genotype.

Numeracy. A validated eight-item scale assessed numeracy (i.e., understanding of numbers and probabilities) at the outset of the blood draw session. The scale combined multiple choice items (e.g., “Which of the following numbers represents the biggest risk of getting a disease?”) with items requiring written responses, such as “If person A’s risk of getting a disease is 1 in 100 in ten years, and person B’s risk is double that of person A’s, what is B’s risk?” (Lipkus, Samsa, & Rimer, 2001). A numeracy score equaled the number of correct responses on this scale, ranging from 0 to 8. Item non-response on multiple choice items were considered incorrect (up to 2 instances per item) except for three people in the third trial whose numeracy scores were imputed because all data on this scale was missing.

Cognitions

Interest in genetic test. A single item at intake asked “in general, do you think you would be interested in having a genetic test to assess your chance of developing AD?” Response options included “yes,” “no,” and “maybe.” Due to small number of

participants responding with anything other than “yes,” “no” and “maybe” responses are collapsed to simplify most analyses.

Perceived AD seriousness. A single item administered at intake asked to rate their agreement to the statement “Alzheimer disease is the worst disease I can think of” on a 5-point scale from strongly disagree (1) to strongly agree (5). Non-response at intake (1 instance) occurred for one participant who was neither self-referred nor systematically recruited.

Perceived benefits and perceived risks and limitations. The written questionnaire measured *perceived benefits* and *perceived risks and limitations* of genetic susceptibility testing for AD using scales developed from research on genetic testing for hereditary breast and ovarian cancer and implemented in subsequent studies of attitudes about AD susceptibility testing, including the first REVEAL Study trial (Lerman et al., 1996; Lerman, Seay, Balshem, & Audrain, 1995; Roberts et al., 2003). Questionnaires included a section that offered eleven reasons “why someone might take a genetic test for AD” (benefits), such as “to seek information on preventative measures,” “the need to make arrangements for my long-term care,” and “curiosity.” A separate section offered ten reasons “why someone might not want to take a genetic test for AD” (risks and limitations), such as “there is no way to cure or prevent AD,” “the test does not give me a definite answer about whether I might get AD or not,” and “the results could affect my health insurance.” Participants rated the importance of each reason to them on a scale of 1 (not at all) to 5 (extremely).

Benefits scores and risks and limitations scores ranged from 1-5 equaling the mean of responses on each scale, with higher scores indicating greater perceived benefits

and greater perceived risks and limitations, respectively. Internal consistency was strong for each measure: Cronbach's $\alpha=.82$ for the benefits scale and .81 for the risks and limitations scale.

Causal beliefs. Items assessing causal beliefs were replicated from research on AD illness representations (Roberts & Connell, 2000). The written questionnaire assessed *genetic causal beliefs* with a single item where participants rated the importance of "genetics/heredity" for increasing one's risk of AD. Scores ranged from 1 (not important) to 5 (very important). Similarly, a measure of *lifestyle causal beliefs* asked participants to rate the importance of "lifestyle (e.g., diet, exercise, smoking)" in increasing one's risk of AD, also on a 1-5 scale from not important to very important.

AD control. Measures in the written questionnaire assessing AD control beliefs differed by REVEAL Study trial. In the second trial, participants rated their agreement from 1=strongly disagree to 5=strongly agree with four statements adapted from the Multidimensional Health Locus of Control Scale (Wallston & Wallston, 1978): "no matter what I do, if I am going to get AD, I will get it," "if I take care of myself, I can avoid AD," "there are medicines, foods, or personal behaviors that can reduce severity of AD," and "if I have a form of a gene that increases my risk for AD, I can take actions that will help prevent it." In the third trial, participants rated their agreement using the same response options with six statements adapted from the Revised Illness Perceptions Questionnaire (Moss-Morris et al., 2002): "there is a lot the person can do to control his or her symptoms of AD," "what the person does can determine whether his or her AD gets better or worse," "the course of the Alzheimer's disease depends on the person," "nothing the person does will affect his or her Alzheimer's disease," "the person has the

power to influence his or her Alzheimer's disease," and "the person's actions will have no effect on the outcome of his/her Alzheimer's disease." Summary measures equaled the mean of responses on scale items (reverse scoring where appropriate), with scores standardized to permit analyses across trials. Internal consistency of the scale in the second trial was borderline (Cronbach's $\alpha = .65$) but strong in the third trial (Cronbach's $\alpha = .80$).

Coping self-efficacy. During the telephone interview, study administrators asked participants for open-ended responses to the question "On a scale of 0 to 100%, how certain are you that you would be able to cope with receiving a genetic test result that increased your chance of developing Alzheimer's disease?" where 0% represented "I am certain that I cannot cope" and 100% represented, "I am certain that I can cope."

Emotional factors

AD concern. The intake instrument assessed AD concern using a scale implemented in prior research on FDRs of AD patients (Roberts & Connell, 2000). Participants rated their agreement on 5-point scales on the following four items: "I am concerned that I will develop AD," "I am concerned that I will develop Alzheimer disease in the next 5 years," "I would like to know if I am going to develop AD at some point later in my life," and "I believe that I will someday develop AD." Internal consistency of this scale was borderline (Cronbach's $\alpha = .60$).

AD worry. During the phone interview, a single item asked, "Presently, how often do you think about getting Alzheimer's disease?" Participants responded on a 4-point scale from not at all/rarely to a lot.

Data analysis

Two-sided independent samples t-tests, Wilcoxon rank sum tests, and chi-squared tests compared the demographic profile of the self-referred cohort against the systematically recruited cohort as well comparing the population that dropped out before testing to the retained sample. McNemar tests and generalized estimating equations compared the efficacy of education on individual knowledge items administered both before and after education, and paired t-tests compared the total number of correct responses before education with the total number of correct responses afterwards. Chi-squared analyses and logistic regression compared whether self-referred participants were more likely to answer correctly than systematically recruited participants on individual knowledge items administered only after education, and linear regression compared referral cohorts on the summed number of correct responses on the same items.

Paired t-tests compared post-education AD susceptibility perceptions to pre-test perceptions. A two-proportion tested the hypothesis that self-referred participants were more likely to change AD susceptibility perceptions than systematically recruited participants following education, and independent samples t-tests examined whether quantitative changes in susceptibility perceptions varied by referral cohort. Independent-samples t-tests examined how psychosocial constructs correlated with study dropout. Chi-squared tests compared overall study attrition by referral cohort, and logistic regression examined study dropout after controlling for differences on demographic and psychosocial factors. Finally, chi-squared tests compared reasons for dropout by referral cohort.

Multivariable analyses treated income as a continuous variable (0= \leq \$10K, 5=\$100+) rather than a categorical variable based on model comparisons showing no difference in overall fit. Where expected cell sizes were below 5, I ran chi squared tests using Monte Carlo tests with 2,000 replicates (Hope, 1968). I imputed item non-response on most items using fully conditional specification using R package *mice* 2.12 (van Buuren & Groothuis-Oudshoorn, 2011). Models for each imputed variable included the following predictors: referral status, outcome variables of focus in this paper, demographic characteristics including genetic knowledge and numeracy, cognitions and emotions of focus in these analyses, and stage of study dropout. I ran 20 iterations to create 5 imputed datasets, and used rules developed by Rubin (1987) to pool estimates and variances from imputed datasets and rules developed by Meng and Rubin (1992) to conduct Wald tests to compare linear regression models and the likelihood ratio test to compare logistic regression models. Of note, I did not impute knowledge items for participants who failed to complete the post-education questionnaire because imputation models failed to converge on those items. All analyses were conducted using R version 2.15.0 for Windows (R Development Core Team, 2011).

RESULTS

Study sample prior to offer of education

Sample demographics among participants who were offered pretest education are presented in Table 9. The self-referred cohort was younger than the systematically recruited cohort, had higher household incomes and was more likely to be employed, and had a lower percentage of African Americans. Differences were also apparent in the composition of the self-referred and systematically recruited cohorts by study site and

study round, with a greater percentage of systematically recruited participants coming from the Boston site and the second trial and a greater percentage of the self-referred cohort coming from the Weill School of Medicine, the University of Michigan, and the third trial. Differences in numeracy by referral cohort were not evident: self-referred participants correctly answered 6.8 of 8 items correctly compared to 6.6 among systematically recruited participants ($t=1.25$, $p=.21$).

Impact of education on knowledge and susceptibility perceptions

Table 10 summarizes performance on knowledge items administered prior to and after education. About half of participants did not know, prior to education, that *APOE* testing did not provide definitive information about future AD onset. In fact, 5% of participants responded “yes” to the question, “Can the *APOE* genetic test predict with certainty whether or not a person will get AD?” and 4% responded that having an $\epsilon 4$ allele made it certain that a person would develop AD. Table 10 also shows that education successfully improved understandings for both systematically recruited and self-referred participants. Overall, self-referred participants answered 2.6 of the four repeated items correctly prior to education and 3.5 items correctly afterwards ($t=17.5$, $p<.001$) whereas systematically recruited participants answered 2.6 items correctly at baseline on average and 3.3 correctly afterwards ($t=9.2$, $p<.001$).

Baseline knowledge was comparable in the self-referred and systematically recruited cohorts, but data suggests that self-referred participants were more likely to benefit from education than systematically recruited participants. Although analyses of knowledge items administered only after education showed no differences by referral cohort (see Table 11), analysis of knowledge items administered both before and after

education shows that self-referred participants were more likely to revise their understandings of whether APOE can predict AD onset with certainty. Generalized estimating equations controlling for age, sex, race, numeracy and education show that self-referred participants had 1.99 times greater odds than systematically recruited participants (95% CI: 1.14-3.49, $p=.016$) of correcting their answers to “Can the APOE genetic test predict with certainty whether or not a person will get AD?”, and 1.92 times greater odds (95% CI: .98-3.74, $p=.056$) of correcting their answers to “How does having an APOE-4 gene affect the changes that someone will get AD?” Changes to other repeated knowledge items did not differ by referral cohort.

Hypothesized differences on changes to susceptibility perceptions were not observed, however, as an equal proportion of self-referred and systematically recruited participants reported changes to AD susceptibility. Fifty-nine percent of both referral cohorts reported changes to AD susceptibility perceptions of at least 5%. In fact, AD susceptibility perceptions dropped by roughly equal amounts within both cohorts: self-referred participants reported AD susceptibility of 40.6% on average prior to education and 35.2% after education ($t=5.46$, $p<.001$), whereas systematically recruited participants reported AD susceptibility of 40.2% on average prior to education and 36.7% afterwards ($t=2.03$, $p=.044$).

Uptake of testing and demographic and psychosocial correlates

Data supported the hypothesis that self-referred participants are more likely to follow through with testing than systematically recruited participants. A comparison of the percentages of each cohort completing various stages of the study is presented in Figure 6. Nearly half of systematically recruited participants dropped out before AD risk

and genotype disclosure compared to only about 30% self-referred participants ($\chi^2 = 18.9$, $p < .001$). However, differences in test uptake were not evident among the sample that remained in the study through the offer of education. Twelve per cent of these self-referred participants dropped out before risk assessment and genotype disclosure compared to 15% of the systematically recruited cohort ($\chi^2 = 1.6$, $p = .11$).

Bivariate analyses identified a number of demographic factors that were correlated with uptake of testing, as presented in Table 12. Across cohorts, individuals with greater household income were more likely to follow through with testing, as were participants at the Weill School of Medicine and University of Michigan sites. Within the self-referred cohort, participants who were older or more educated were more likely to follow through with testing, and participants self-identifying as African American were less likely to follow through with testing. The same associations were not evident within the systematically recruited cohort.

Bivariate analyses of psychosocial factors also identified a few that were correlated with test uptake. Other explored factors are summarized in Table 13. Participants in both cohorts who perceived greater risks and limitations to testing were more likely to drop out before risk disclosure, as were participants who had lower self-efficacy about their ability to cope with learning that they were at increased AD risk due to their genetics. Systematically recruited participants with greater AD concern were more likely to drop out before results disclosure. No other factors reached statistical significance.

Table 14 presents the results of a logistic regression model predicting uptake of testing after controlling for factors that both varied by referral cohort, as identified in the

prior paper, and were predictive of uptake in bivariate analyses: age, income, race, site, and AD concern (marginally non-significant at baseline). Older age, greater household income, and lower AD concern were associated with greater likelihood of test uptake. No independent effect of referral status was evident. Of note, associations between self-identified race and uptake of testing virtually disappeared after controlling for those other covariates. In fact, African Americans were no more likely to drop out of the study than other racial groups after controlling for just income (OR=1.45, 95% CI=.81-2.61) whereas income was still significant (OR=.69, 95% CI=.58-.82 per one-category increase in income).

Reasons for dropout before test uptake were not recorded for many participants who dropped out after being offered education (46%). Among the 31 self-referred and 11 systematically recruited participants who *did* provide reasons, the main ones were concerns about emotional wellbeing (33%) and demands of study participation (24%), followed by concerns about privacy, confidentiality, and potential discrimination (12%), personal or family health problems (12%), a lack of prevention options (10%), and limitations of test information or a lack of interest (7%). Twelve participants were screened out because they scored above eligibility cutoffs on baseline anxiety or depression or scored below eligibility cutoffs on neuropsychology tests. Screen out rates did not vary by referral cohort ($\chi^2=1.4$, $p=.246$).

DISCUSSION

This is one of few analyses to explore how the processes used to recruit and enroll participants into genetic susceptibility testing research affect the influence of pretest education and subsequent uptake of testing. The analyses presented here expands upon

prior work on the REVEAL Study that suggested that self-referred participants are more likely to follow through with testing by presenting a more holistic description of how self-referral affects the impact of pre-test education on knowledge and susceptibility perceptions, and by exploring the association between self-referral and important factors that may predict uptake of testing.

As found in prior analyses of data from the second REVEAL Study trial, pretest education was effective at correcting misperceptions about AD and genetic susceptibility testing (Roberts et al., In press). Its effectiveness was greater among the self-referred cohort, particularly on items asking whether testing was deterministic. The analyses presented here raise the concern that studies that enroll participants primarily through self-referral and then examine educational strategies may exaggerate their effectiveness. One explanation is that self-referred individuals were more motivated to receive the information and, as might be suggested by the Elaboration Likelihood Model, more likely to centrally process the educational materials and retain educational messages than systematically recruited individuals. In addition, genetic counselors and other professionals providing pretest education need to take care and ensure individuals who are pursuing testing in response to an offer or referral are internalizing important educational points, particularly around limitations to the tests' predictive powers.

Predictions about how pre-test education changes susceptibility perceptions were unsupported by the data, however, as both self-referred and systematically recruited participants changed their susceptibility perceptions for AD at similar rates and by similar amounts after education. Certainly, one explanation is that hypotheses were incorrect, and self-referred participants were no more motivated or capable of processing the

information than systematically recruited participants. Another explanation is that the susceptibility information conveyed in pretest education was accompanied by numerous caveats, compromising its persuasive power. Although pretest education communicated specific numeric risks for AD among the general population (10-15%) well below what REVEAL participants were reporting at baseline, pretest educational materials also presented a number of factors affecting those numbers, including female gender, African American racial identification, and having an affected FDR. The last factor is particularly important, given eligibility criteria stipulated that all participants in the second trial and three-quarters of participants in the third trial had an affected FDR. In fact, mean susceptibility perceptions after education among all participants (35%) were surprisingly close to actual risk estimates disclosed to participants after genotyping (33%), and prior published work shows that prior to education, women and $\epsilon 4$ carriers rated their AD risk higher than men and non-carriers, respectively (Linnenbringer, Roberts, Hiraki, Cupples, & Green, 2010). It is possible that participants' experiences with AD were far more influential for shaping susceptibility perceptions than educational materials, an assertion supported by work showing that nearly half of participants who can accurately recall the risk estimates provided by the REVEAL Study still perceive their risk as something different (Linnenbringer et al., 2010). Alternatively, participants may have researched their AD risk prior to enrolling in the REVEAL Study and known that their personal risk was much higher than the population risks quoted in educational materials.

Hypotheses with respect to uptake of testing were only partially supported. Although self-referred participants at intake were far more likely to follow through with testing, differences were not statistically significant after participants had reached the

stage of being offered education. Self-referral introduced demographic and emotional differences documented in the prior paper, and analyses presented here identified a number of those factors to be associated with lower study dropout after education had been offered. Specifically, self-referred participants tended to have greater incomes and were less likely to self-identify as African American (although the impact of race may be confounded by income). Notably, clinical trials in general tend to enroll populations skewed towards those of high socioeconomic status (Baquet, Commiskey, Daniel Mullins, & Mishra, 2006; Sateren et al., 2002), while African Americans are typically underrepresented in genetic and clinical research (Ford et al., 2006; McQuillan et al., 2003; Murthy, Krumholz, & Gross, 2004). Greater dropout rates among lower-income participants and African Americans may have been driven by factors common to research in general rather than the REVEAL Study and AD genetic susceptibility testing in particular.

Interestingly, some of the other factors that were associated with self-referral were actually associated with a greater likelihood of study dropout. Age is one of these factors. Typically, younger individuals, particularly those under the age of 65, are more likely to participate in clinical trials than older adults (Hutchins, Unger, Crowley, Coltman Jr., & Albain, 1999; Lewis et al., 2003; Murthy et al., 2004). However, studies of genetic susceptibility testing for hereditary breast cancer testing (Donovan & Tucker, 2000; Kessler et al., 2005) and DTC genetic testing for multiple common, complex conditions (Bloss et al., 2010) have found more favorable attitudes among older individuals. It may be that the referral processes facilitating self-referral are more appropriate for younger adults, whereas motivation for testing is actually greater among older individuals.

Concern is another factor that was marginally greater among self-referred participants and was also associated with dropout before test uptake. Interestingly, participants with greater concern were marginally *less* likely to drop out of the study before the offer of pretest education. One explanation is that participants with greater concern drop out after education because they learn about the lack of proven preventive options or the test's limited predictive power. Substantial evidence suggests that emotions such as fear can motivate behaviors such as screening for disease risk, but only when effective prevention strategies exist. In contrast, fear combined with an absence of efficacious options to reduce disease risk can lead to avoidance behaviors (Witte, 1992). Concerns about emotional wellbeing were the most commonly cited reason for dropout when a reason was given, and anecdotal evidence suggests that many participants enroll in the REVEAL Study with the hopes that, as a research study, it may have knowledge of cutting edge prevention options not commonly known to the greater public (Christensen et al., 2011). Upon learning during education that the study did not have access to such options, high-concern participants may have made informed decisions to forego testing and avoid psychological risks.

Given the above points, it is not surprising that coping self-efficacy was higher among participants who ultimately followed through with testing, even if it did not vary by referral cohort. Although self-efficacy about one's ability to cope with results has not been examined in other studies of genetic susceptibility testing, self-efficacy about other aspects of testing, particularly understanding test information, has been found in other studies of genetic susceptibility testing (Manne et al., 2007; McBride et al., 2009). Much of the discussion about genetic susceptibility testing has centered on the utility (or lack

thereof) of testing (Burke, Laberge, & Press, 2010; Goldman et al., 2011; Grosse, McBride, Evans, & Khoury, 2009). The findings from the analyses presented here highlight that uptake of genetic susceptibility testing may be just as contingent upon the ability of individuals to process genetic information effectively and safely.

Participants who followed through with testing and received results also tended to perceive fewer risks and limitations to testing, although that factor was also not correlated with referral processes. Notably, pretest education stressed how employers or insurance companies could use potentially use test results to deny insurance coverage or change rates, and analyses of data from the second REVEAL Study trial showed that concerns about employment, health insurance, or interpersonal discrimination increased slightly among those who ultimately received AD risk and *APOE* genotype disclosure (Christensen et al., 2011). It is possible that many individuals were unaware of these risks until educated and afterwards made informed decisions to forego testing. If so, the passage of the Genetic Information Non-Discrimination Act (GINA) of 2008, which provides federal protections against employment and health insurance discrimination as a result of genetic testing, may result in greater uptake of *APOE* testing for AD risk. It should be noted, though, that GINA does not cover long-term care insurance.

Notably, an independent effect of referral processes on uptake of testing was not observed. If the act of self-referring to the REVEAL Study itself primes individuals to be more motivated to follow through with testing, the effect appears to be far too subtle to result in differences in test uptake. The supposition that self-referral might itself cause individuals to have greater motivation for testing stemmed from Self Determination Theory and its assertion that processes that nurture autonomy increase intrinsic

motivation (Ryan & Deci, 2000). Systematic recruitment is a very different process from mandatory screening, though, and still maintains an environment where testing is completely voluntary. It is probable that differences in test uptake by referral cohort observed from intake are almost entirely the result of *who* enrolled rather than *how* they enrolled.

The analyses presented here may assist the interpretation of findings on genetic susceptibility testing for common, complex conditions more generally, as a number of important studies of genetic susceptibility testing, such as the Scripps Genomic Health Initiative (Bloss et al., 2010) and the Coriell Personalized Medicine Collaborative (Gordon et al., 2010), have largely collected data from self-referred samples. Admittedly, the susceptibility testing offered in the REVEAL Study differs from testing in these other initiatives and from genetic risk assessments more broadly in important ways, including having greater predictive power than most genetic markers being identified now and providing information about a condition with no proven prevention options. Most individuals believe lifestyle, social, and environmental factors contribute to AD risk, however (Roberts, 2000), and REVEAL Study participants cite learning information about prevention as the main reason to undergo testing, even after being educated on AD risk factors through the testing process (Christensen et al., 2011). *APOE* genotyping for AD risk is similar to single-disease genetic susceptibility testing for other conditions from the perspective of potential test recipients.

Moreover, understanding how individuals respond to *APOE* genotyping for AD risk may be important in itself given trends in genetic testing more broadly. As mentioned earlier, a number of DTC genetic testing companies have recently

incorporated *APOE* genotyping for AD risk into their panels. In addition, recent research raises hopes that improving health behaviors earlier in life (Lee et al., 2010; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010) or tailoring therapies to attack specific disease pathways (Cramer et al., In press; Liu et al., 2012) or genotypes (Mihaescu et al., 2010) will be more effective for reducing AD risk. If proven methods for AD prevention or risk reduction emerge, clinical susceptibility testing for AD risk will likely become more common.

Limitations

A number of important limitations exist, including those noted in the prior paper. Important differences in sampling frames exist, as referral processes encouraging self-referral often targeted broad audiences through media like newspaper whereas systematic recruitment tended to target populations with connections to AD treatment or research, such as neurology clinic families or members of AD research registries. Differences resulting from *who* was targeted for recruitment are difficult to distinguish from differences resulting from *how* they were enrolled, which is the focus of these analyses.

Another limitation is an inability to clearly differentiate the impact of pretest education. These analyses were conducted on individuals who were offered education. Most participants offered in-person education actually attended the sessions, but little is known about whether or not participants reviewed mailed educational materials; and because reasons for dropout were not ascertained for most participants who dropped out of the study, it is impossible to draw conclusions about how much of the study attrition was attributable to demands of research more generally versus dropout due to concerns about AD susceptibility testing or a lack of interest in that testing specifically.

Lastly, the generalizability of findings to other testing contexts may be limited and needs to be considered with care. In addition to the dissimilarities between AD and other common diseases addressed earlier, REVEAL Study testing focused on testing of a single gene for a single disease testing. Trends are to use multi-gene panels to assess risk for multiple diseases simultaneously. Disease-specific psychosocial factors examined in these analyses have been found to be important in other studies of susceptibility tests examining genes with strong predictive power, but uptake of panel testing of low-penetrance markers may be less reliant on illness perceptions. Uptake of testing in the Multiplex Initiative, for instance, was much more contingent upon skills like self-efficacy for understanding genetic information or recognition of health habits that need improvement than perceived risks for disease (McBride et al., 2009).

Conclusions

Results from these analyses show that self-referred participants in genetic susceptibility testing research are more likely to retain through the earliest phases of research, but are no more likely to follow through with testing than systematically recruited participants once education is offered. Results do suggest, however, that self-referred participants may be more likely to internalize certain elements of pretest education, although the differential impact of education on beliefs about disease such as risk perceptions may be minimal.

TABLES

Table 9. Descriptive statistics of REVEAL Study participants offered pretest education by referral cohort.

| | Systematically Recruited (n=162) | Self-Referred (n=439) | Total (n=601) | P |
|--|--|--------------------------|------------------|-----------------|
| <i>Continuous/ordinal variables: mean (sd)</i> | | | | |
| Age in years | 61.3 (12.0) | 56.7 (11.5) | 57.9 (11.8) | <.001 |
| Years of education | 16.1 (2.9) | 16.3 (2.4) | 16.3 (2.6) | .263 |
| # of affected relatives | 1.6 (1.2) | 1.8 (1.3) | 1.7 (1.2) | .143 |
| Median income | \$50-69K | \$70-99K | \$70-99K | .005 |
| <i>Categorical variables: n (%)</i> | | | | |
| Black/African American | 47 (29.0%) | 60 (13.7%) | 107 (17.8%) | <.001 |
| Male | 60 (37.0%) | 152 (34.6%) | 212 (33.8%) | .650 |
| Employed part/full time | 81 (50.0%) | 290 (66.2%) | 371 (61.8%) | <.001 |
| ε4 carrier* | 46 (33.6%) | 144 (37.1%) | 190 (36.2%) | .524 |
| Site by referral cohort | | | | <.001 |
| Boston University | 77 (47.5%) | 107 (24.4%) | 184 (30.6%) | |
| Case Western Reserve | 35 (21.6%) | 106 (24.1%) | 141 (23.5%) | |
| Howard University | 36 (22.2%) | 78 (17.8%) | 114 (19.0%) | |
| Weill School of Medicine | 9 (5.6%) | 79 (18.0%) | 88 (14.6%) | |
| University of Michigan | 5 (3.1%) | 69 (15.7%) | 74 (12.3%) | |
| Trial by referral cohort | | | | .005 |
| 2 nd Trial | 101 (62.3%) | 215 (49.0%) | 316 (52.6%) | |
| 3 rd Trial | 61 (37.7%) | 224 (51.0%) | 285 (47.4%) | |
| Randomization arm by trial and referral cohort | | | | |
| 2 nd Trial | | | | .371 |
| Extended Protocol | 29 (28.7%) | 79 (36.7%) | 108 (34.2%) | |
| Condensed Protocol (GC) | 36 (35.6%) | 67 (31.2%) | 103 (32.6%) | |
| Condensed Protocol (MD) | 36 (35.6%) | 69 (32.1%) | 105 (33.2%) | |
| 3 rd Trial | | | | |
| AD+CVD disclosure | 30 (49.2%) | 108 (48.2%) | 138 (48.4%) | .992 |
| Phone disclosure | 22 (36.1%) | 115 (51.3%) | 137 (48.1%) | .049 |

* Determined through genotyping among participants who provided blood samples (137 systematically recruited participants, 388 self-referred participants, 525 total).

Table 10. Comparison of knowledge prior to and after education among participants who received AD risk assessments with *APOE* genotype disclosure: number and percent answering individual items correctly. Excludes 3 participants who answered no data on the post-ed questionnaire.

| Item | <i>Systematically Recruited</i> | | | <i>Self-Referred</i> | | | <i>Total</i> | | |
|--|---------------------------------|--------------------|-------|----------------------|--------------------|-------|-------------------|--------------------|-------|
| | Pre Ed (n=162) | Post Ed (n=144) | p* | Pre Ed (n=439) | Post Ed (n=402) | p* | Pre Ed (n=601) | Post Ed (n=546) | p* |
| Can the APOE genetic test predict with certainty whether or not a person will get AD? | 83 (51.2%) | 107 (74.3%) | <.001 | 235 (53.5%) | 336 (83.6%) | <.001 | 318 (52.9%) | 443 (81.1%) | <.001 |
| How does having an APOE-4 gene affect the chances that someone will get AD? | 92 (56.8%) | 124 (86.1%) | <.001 | 261 (59.5%) | 371 (92.3%) | <.001 | 353 (58.7%) | 495 (90.7%) | <.001 |
| What is the average person's lifetime risk of getting AD? | 78 (48.1%) | 103 (71.5%) | <.001 | 218 (49.7%) | 303 (75.4%) | <.001 | 296 (49.3%) | 406 (74.4%) | <.001 |
| How are people's chances of developing AD different if they have a parent or sibling who has or had the disease? | 161 (99.4%) | 144 (100%) | NA | 437 (99.5%) | 402 (100%) | NA | 598 (99.5%) | 546 (100%) | NA |

* McNemar's test of marginal homogeneity testing the hypothesis that the proportion of participants not answering correctly at baseline but answering correctly after education is greater than the proportion of participants answering correctly at baseline and then not being correct after education.

Table 11. Performance on knowledge items administered only after education stratified by referral cohort: number and percentage answering correctly. Excludes 3 self-referred participants who did not answer any items on the post-education questionnaire.

| <i>Items administered only after education</i> | <i># (%) Correct After Education</i> | | | <i>p</i> [*] |
|--|--------------------------------------|-----------------------------|--------------------------|-----------------------|
| | <i>Sys Rec (n=144)</i> | <i>Self-Ref (n=402)</i> | <i>Total (n=546)</i> | |
| Which of the following factors will be used to calculate your personal risk assessment? | 113 (78.5%) | 339 (84.3%) | 452 (82.8%) | .110 |
| Men are more likely to develop Alzheimer's disease than women | 126 (87.5%) | 358 (89.1%) | 484 (88.6%) | .614 |
| In most cases, when do the first signs of Alzheimer's disease usually occur? | 129 (89.6%) | 371 (92.3%) | 500 (91.6%) | .316 |
| A genetic test result that does not include a copy of the risk-increasing form of the APOE gene means that there is a 0% chance of developing AD | 137 (95.1%) | 382 (95.0%) | 519 (95.1%) | .957 |
| Drugs are available to prevent Alzheimer's disease | 137 (95.1%) | 389 (96.8%) | 526 (96.3%) | .372 |

* Chi-squared test assessing whether the likelihood of participants answering correctly after education depended on whether the participant had self-referred or was systematically recruited into the study.

Table 12. Demographic profile of participants who dropped out before completion of testing compared with participants who followed through with testing, stratified by referral cohort.

| | <i>Systematically Recruited</i> | | | <i>Self-Referred</i> | | | <i>Total</i> | | |
|--|---------------------------------|----------------------|-------------|----------------------|----------------------|-----------------|-------------------|----------------------|-----------------|
| | Dropped (n=25) | Disclosed (n=137) | p | Dropped (n=51) | Disclosed (n=388) | p | Dropped (n=76) | Disclosed (n=525) | p |
| Age in years | 58.9 (12.8) | 61.7 (11.8) | .284 | 54.3 (12.1) | 57 (11.4) | .112 | 55.8 (12.4) | 58.2 (11.7) | .093 |
| Education in years | 15.1 (3.4) | 16.2 (2.8) | .067 | 14.7 (2.6) | 16.5 (2.3) | <.001 | 14.8 (2.8) | 16.5 (2.5) | <.001 |
| # of affected relatives | 1.8 (1.3) | 1.6 (1.2) | .233 | 1.8 (1.2) | 1.8 (1.3) | .846 | 1.8 (1.2) | 1.7 (1.2) | .472 |
| Median income | \$50-69K | \$50-69K | .055 | \$30-49K | \$70-99K | <.001 | \$30-49K | \$70-99K | <.001 |
| Black/African American | 7 (28.0%) | 40 (29.2%) | .903 | 15 (29.4%) | 45 (11.6%) | <.001 | 22 (28.9%) | 85 (16.2%) | .007 |
| Male | 7 (28.0%) | 53 (38.7%) | .309 | 12 (23.5%) | 140 (36.1%) | .076 | 19 (25.0%) | 193 (36.8%) | .045 |
| Employed part/full time | 8 (32.0%) | 73 (53.3%) | .050 | 30 (58.8%) | 260 (67.2%) | .235 | 38 (50.0%) | 333 (63.5%) | .023 |
| Site | | | | | | | | | |
| Boston University | 14 (56.0%) | 63 (46.0%) | .238 | 12 (23.5%) | 95 (24.5%) | .067 | 26 (34.2%) | 158 (30.1%) | .020 |
| Case Western Reserve | 4 (16.0%) | 31 (22.6%) | | 12 (23.5%) | 94 (24.2%) | | 16 (21.1%) | 125 (23.8%) | |
| Howard University | 7 (28.0%) | 29 (21.2%) | | 16 (31.4%) | 62 (16.0%) | | 23 (30.3%) | 91 (17.3%) | |
| Weill Sch of Medicine | 0 (0%) | 9 (6.6%) | | 5 (9.8%) | 74 (19.1%) | | 5 (6.6%) | 83 (15.8%) | |
| University of Michigan | 0 (0%) | 5 (3.6%) | | 6 (11.8%) | 63 (16.2%) | | 6 (7.9%) | 68 (13%) | |
| Trial | | | | | | | | | |
| 2nd Round | 16 (64.0%) | 85 (62.0%) | .853 | 28 (54.9%) | 187 (48.2%) | .368 | 44 (57.9%) | 272 (51.8%) | .321 |
| 3rd Round | 9 (36.0%) | 52 (38.0%) | | 23 (45.1%) | 201 (51.8%) | | 32 (42.1%) | 253 (48.2%) | |
| Randomization – 2 nd Trial (3 arms) | | | | | | | | | |
| Extended | 5 (31.2%) | 24 (28.2%) | .278 | 13 (46.4%) | 66 (35.3%) | .520 | 18 (40.9%) | 90 (33.1%) | .481 |
| Condensed – GC | 3 (18.8%) | 33 (38.8%) | | 8 (28.6%) | 59 (31.6%) | | 11 (25.0%) | 92 (33.8%) | |
| Condensed – MD | 8 (50.0%) | 28 (32.9%) | | 7 (25.0%) | 62 (33.2%) | | 15 (34.1%) | 90 (33.1%) | |
| Randomization – 3 rd Trial (2X2 factorial design) | | | | | | | | | |
| Pleiotropic information | 7 (77.8%) | 23 (44.2%) | .073 | 12 (52.2%) | 96 (47.8%) | .688 | 19 (40.6%) | 119 (59.4%) | .188 |
| Phone disclosure | 3 (33.3%) | 19 (36.5%) | 1.00 | 12 (52.2%) | 103 (51.2%) | .933 | 15 (46.9%) | 122 (48.2%) | .886 |

Table 13. Associations between psychosocial factors and study dropout before results disclosure, stratified by referral cohort.

| | <i>Systematically Recruited</i> | | | <i>Self-Referred</i> | | | <i>Total</i> | | |
|---|---------------------------------|----------------------|-------------|----------------------|----------------------|-------------|-------------------|----------------------|-----------------|
| | Dropped (n=25) | Disclosed (n=137) | p | Dropped (n=51) | Disclosed (n=388) | p | Dropped (n=76) | Disclosed (n=525) | p |
| Perceived susceptibility prior to education | 52.1 (4.9) | 39.7 (2.1) | .021 | 39 (3.5) | 40.4 (1.3) | .703 | 43.3 (2.8) | 40.2 (1.1) | .308 |
| Perceived susceptibility after education | 48.6 (8.8) | 36.1 (2.0) | .170 | 38.8 (6.0) | 35 (1.3) | .539 | 41.7 (5.0) | 35.3 (1.1) | .214 |
| Perceived seriousness | 2.92 (.30) | 3.18 (.13) | .430 | 3.37 (.20) | 3.19 (.07) | .376 | 3.22 (.16) | 3.18 (.06) | .817 |
| AD Concern | 3.79 (.17) | 3.34 (.07) | .014 | 3.54 (.09) | 3.50 (.03) | .668 | 3.62 (.08) | 3.46 (.03) | .057 |
| AD Worry | 1.96 (.15) | 1.85 (.06) | .507 | 2.12 (.11) | 2.13 (.04) | .891 | 2.07 (.09) | 2.06 (.03) | .960 |
| Perceived benefits | 3.58 (.16) | 3.56 (.07) | .915 | 3.66 (.10) | 3.52 (.04) | .160 | 3.64 (.08) | 3.53 (.03) | .227 |
| Perceived risks and limitations | 2.17 (.14) | 1.89 (.06) | .063 | 2.14 (.09) | 1.84 (.03) | .002 | 2.15 (.08) | 1.85 (.03) | <.001 |
| Genetic causal beliefs | 4.12 (.18) | 4.02 (.08) | .620 | 4.21 (.12) | 4.1 (.04) | .353 | 4.18 (.1) | 4.08 (.04) | .317 |
| Lifestyle causal beliefs | 3.28 (.24) | 3.48 (.10) | .433 | 3.66 (.16) | 3.42 (.06) | .154 | 3.54 (.13) | 3.44 (.05) | .486 |
| Coping self-efficacy | 79.7 (3.6) | 87.3 (1.5) | .054 | 78 (2.6) | 87.2 (.9) | .001 | 78.5 (2.1) | 87.2 (.8) | <.001 |
| AD Control | -.05 (.22) | .04 (.09) | .703 | -.20 (.14) | 0 (.05) | .154 | -.15 (.12) | .01 (.04) | .177 |

Table 14. Logistic regression model predicting uptake of testing after the offer of education. Covariates are factors that both varied by referral cohort and predicted results uptake in bivariate analyses (n=601).

| | OR (95% CI) | t | p |
|---|------------------|-------|-----------------|
| Intercept | 1.00 (.14-7.08) | .00 | .997 |
| Age (per year) | 1.03 (1.01-1.05) | 2.53 | .012 |
| Income category | 1.48 (1.24-1.76) | 4.38 | <.001 |
| Black or African American (ref: any other race) | .80 (.43-1.48) | -.73 | .468 |
| Weill School of Med/U Michigan (ref: other sites) | 1.89 (.92-3.87) | 1.75 | .081 |
| AD Concern | .67 (.47-.96) | -2.19 | .029 |
| Self-referred (ref: systematically recruited) | 1.17 (.66-2.06) | .55 | .586 |

Overall model evaluation

Likelihood ratio test: $F=6.73$, $df=6$, 1.5×10^9 , $p<.001$

Goodness of fit

Hosmer & Lemmeshow test: $\chi^2=14.0$, $df=8$, $p=.082$

FIGURES

Figure 4. Conceptual model tested in Chapter 5.

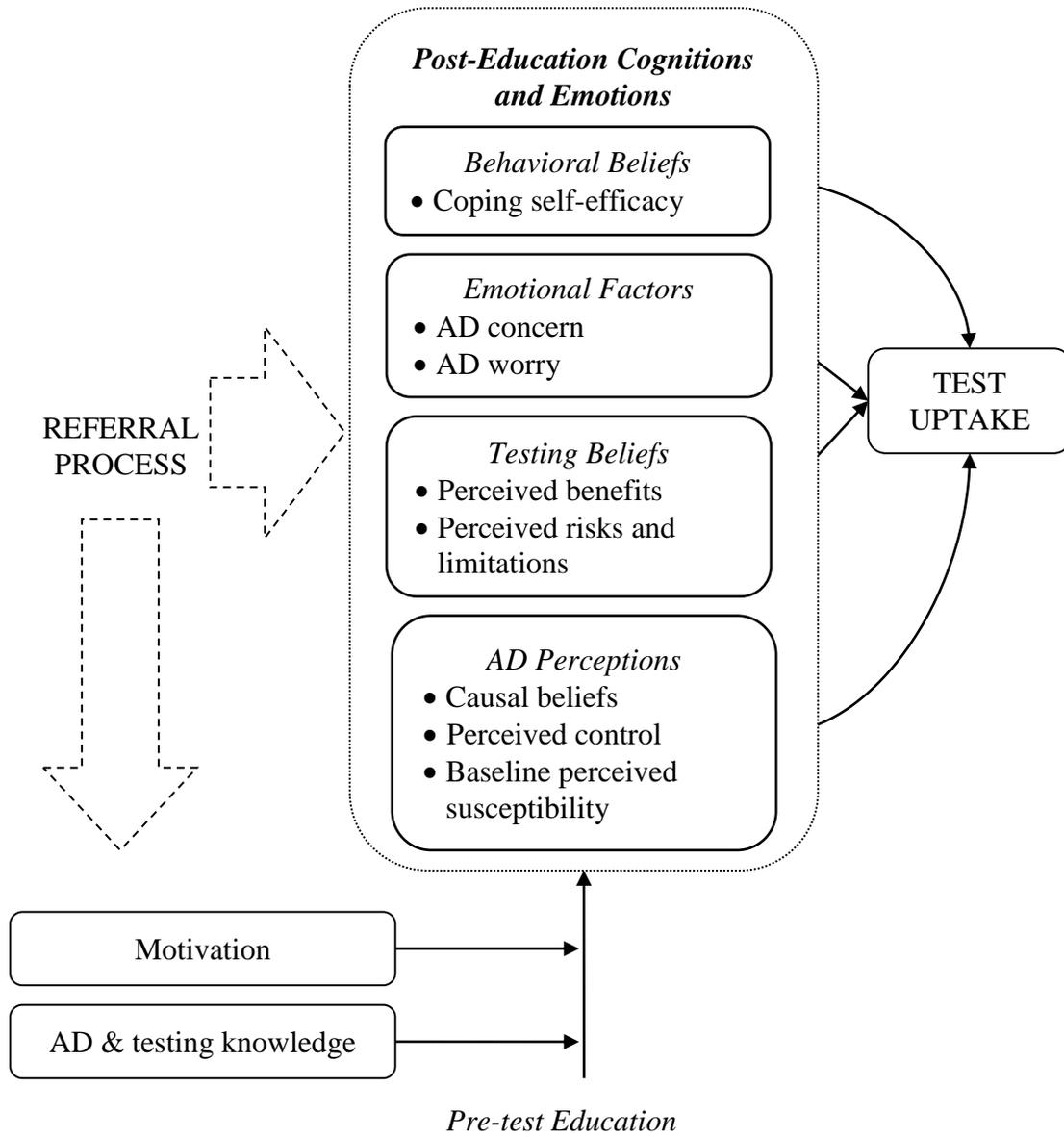


Figure 5. REVEAL Study flow chart, specifying when key psychosocial constructs were measured. Primary outcomes (i.e., test uptake and AD susceptibility perceptions, both pre- and post-education) are identified with an asterisk.

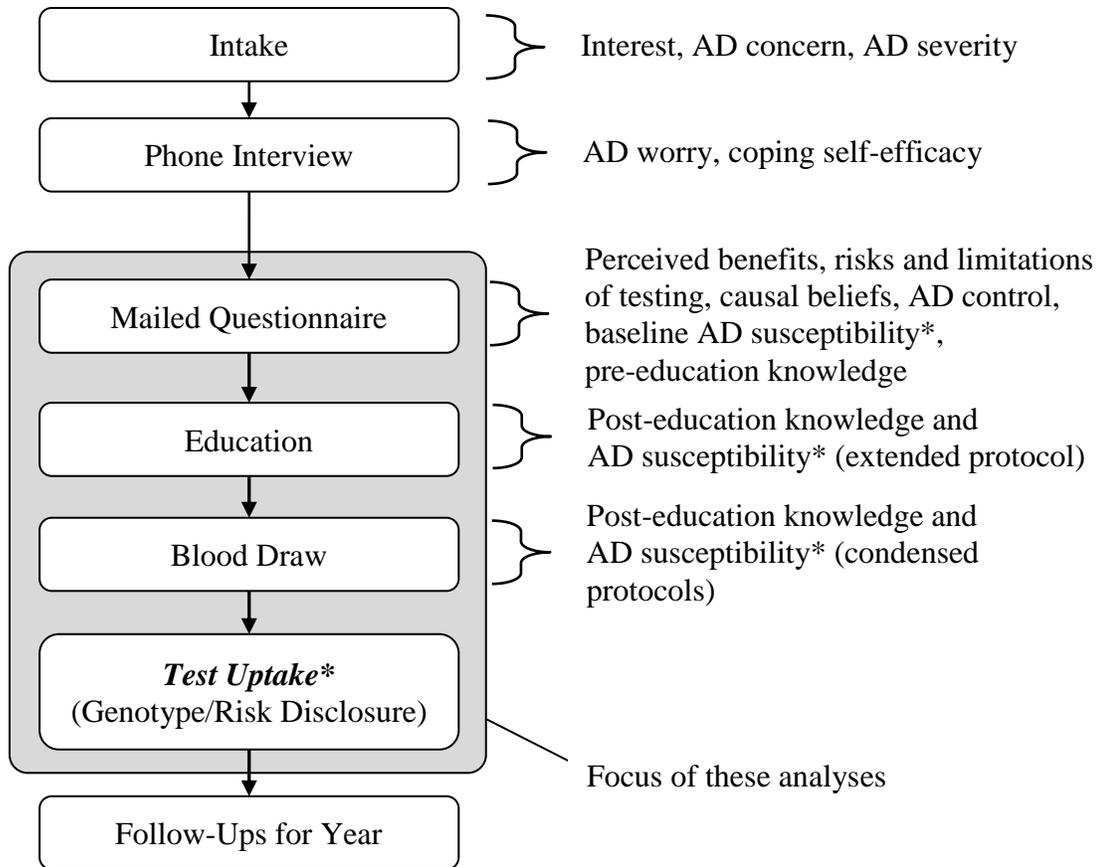
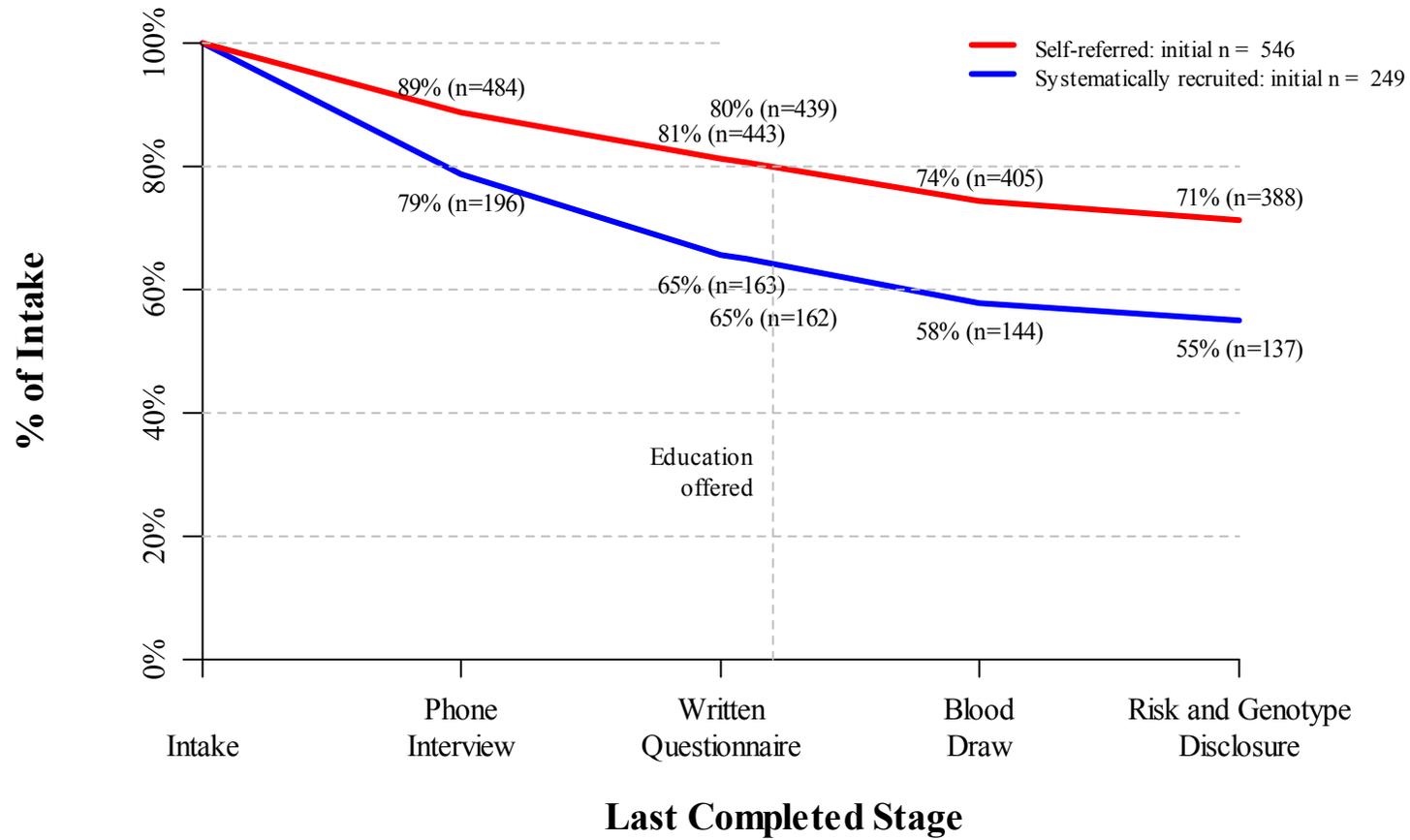


Figure 6. Study retention by stage of study and referral cohort.



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CHAPTER 6

BEHAVIORAL RESPONSES TO GENETIC SUSCEPTIBILITY TESTING

BACKGROUND

The rapid emergence of genetic susceptibility tests for common, complex disease has generated much speculation about whether they can be effective tools for motivating behavior change. Proponents envision a future where testing helps individuals tailor prevention efforts and life decisions in response to indications of increased risk for disease due to inherited factors (Botkin et al., 2010; Collins, Green, Guttmacher, & Guyer, 2003; Evans, 2007; Hogarth, Javitt, & Melzer, 2008; Janssens et al., 2008). However, results from behavioral research to date have suggested a need to temper this optimism. Tests that examine genes associated with high risk for cancer can improve compliance with screening recommendations and increase the likelihood that individuals will follow through with prophylactic surgery decisions (McBride, Koehly, Sanderson, & Kaphingst, 2010). Tests that use genetic markers with less predictive power, however, have demonstrated little ability to motivate individuals to change behaviors such as smoking, sunscreen use, diet, and physical activity (Aspinwall, Leaf, Dola, Kohlmann, & Leachman, 2008; Beery & Williams, 2007; Bloss, Schork, & Topol, 2011; McBride et al., 2010).

Commentators often hold up susceptibility testing for Alzheimer's disease (AD) as an example of the ability of genetic risk assessments to motivate behavior change (Angrist, 2009; Graves, Peshkin, Luta, Tuong, & Schwartz, 2011; O'Daniel, 2010; Turner, Kader, & Xu, 2012). Multiple analyses of how individuals respond to apolipoprotein E (*APOE*) testing to determine AD risk have shown that carriers of the risk-increasing $\epsilon 4$ allele are more likely than non-carriers to report changes to preventive behaviors following AD risk and genotype disclosure, particularly to the use of dietary supplements such as herbal supplements, vitamins, minerals, and antioxidants (Chao et al., 2008; Vernarelli et al., 2010). Furthermore, $\epsilon 4$ carriers are more likely to report changes to advance planning than non-carriers within a year of receiving test results (Taylor et al., 2010; Zick et al., 2005). A number of factors raise concerns about whether these findings will be replicated in other testing contexts, though, including the validity of using self-report to assess outcomes of interest, the lack of well-proven prevention and treatment strategies for AD compared to other common, complex conditions, and the strong association between *APOE* genotype and AD risk compared to the majority of genes included in most test panels.

Another potentially important and overlooked factor is that these studies have primarily examined populations that have self-referred to testing. Important differences may exist in the way these self-referred individuals respond to genetic susceptibility testing compared to systematically recruited individuals. Systematic recruitment can be defined as situations where providers offer testing to specific individuals who may not have been considering it beforehand. Examples include when physicians introduce genetic susceptibility testing studies to families during medical appointments, or when

researchers offer testing to specific individuals through targeted mailings or phone calls. Self-referral, in contrast, can be defined as situations where individuals learn about genetic susceptibility testing studies in a way that did not target them specifically (e.g., through media advertising, through word-of-mouth from acquaintances, from undirected activity on the Internet) and then proactively contact a test provider. Self-referral into genetic susceptibility research can be problematic not only because it precludes the ability of researchers to understand who declines to participate, but also because self-referred participants often respond in very different ways to risk information than systematically recruited individuals. Self-referred populations have been found to be more motivated for behavior change (Binks & O'Neil, 2002) and have greater self-efficacy about preventive health behaviors (Snyder et al., 2008) than systematically recruited populations.

Understanding how self-referral affects behavioral responses to genetic susceptibility testing may be particularly important given how testing is currently offered to the public. Numerous companies are now offering genetic susceptibility testing directly to consumers, primarily through self-referral. The majority of genetic susceptibility tests lack the predictive power to change clinical guidelines for prevention, though. As a result, few protocols for disclosing genetic susceptibility test results make recommendations beyond those that would be provided in the absence of genetic information. Genetic susceptibility testing for AD adds the complication that prevention strategies are generally unproven. If self-referral attracts individuals who are primed to act without being directed, then individuals who self-refer to testing services may be

more likely to initiate health behavior changes than individuals who are enrolled through systematic recruitment.

This paper examines this issue by testing the following hypotheses:

Hypothesis 1: Self-referred participants are more likely to report changes and intentions to change advance planning, use of dietary supplements, and mental activities than systematically recruited participants, after controlling for *APOE* genotype.

Secondary Hypothesis 1: Self-referred participants are more likely to discuss AD preventative measures during genetic risk disclosure than systematically recruited participants, after controlling for *APOE* genotype.

To provide insight about the mechanisms that may explain any observed differences in behavioral outcomes, this paper uses a conceptual model presented in Figure 7. Based on the Common Sense Model of Self Regulation (CSM) (Leventhal, Diefenbach, & Leventhal, 1992), the model assumes that individuals who undergo testing are more likely change future plans and health behaviors if the results increase their perceptions about AD susceptibility and change their perceptions about AD control. The model also assumes that test recipients make changes to advance planning and health behaviors in order to cope with emotional responses to testing, such as concern, worry, distress, and uncertainty. The model expands beyond traditional CSM considerations of negative emotions, acknowledging that testing will generate positive emotional responses in addition to negative ones, and recognizing that positive experiences often lead to different behavioral choices than negative experiences (Berridge & Robinson, 2003; Kahneman & Tversky, 1979; Zikmund-Fisher, Fagerlin, Keeton, & Ubel, 2007). The

model also incorporates the pre-test expectations individuals hold about testing. It posits that individuals who expect testing to aid in decision making will be more likely to report changes to outcomes; and it posits that individuals who expect testing to provide reassurance will have stronger emotional responses than individuals who don't hold such expectations.

Disparities in rates of behavior change between self-referred and systematically recruited individuals may result from demographic, attitudinal, and emotional differences at the point of enrollment and differences in how genetic test results change cognitions and emotions. Earlier analyses showed greater worry and marginally greater concern about AD at enrollment among self-referred participants, but no differences on cognitive factors. Nevertheless, potential differences may exist regarding whether or not participants expect testing to be helpful for decision making. Individuals holding such expectations may be waiting to learn if they have increased genetic risk for disease before making changes to advance planning or health behaviors. Potential differences may exist about whether or not participants expect testing to provide reassurance, also. Individuals expecting reassurance may have stronger emotional responses to learning they are at increased or decreased risk for disease.

Moreover, self-referred test recipients presumably have greater intrinsic motivation to undergo testing than systematically recruited test recipients, and this motivation may affect the strength of cognitive and emotional responses to test results. The Elaboration Likelihood Model, a popular communication theory, asserts that impact of a message is contingent upon the motivation of an individual to receive it (Petty & Cacioppo, 1983). Genetic susceptibility test results, then, may change susceptibility and

control perceptions more among self-referred test recipients than systematically recruited test recipients, and may elicit stronger emotional responses.

Secondary Hypothesis 2: Self-referred participants are more likely to expect testing to aid in decision making and provide reassurance than systematically recruited participants.

Secondary Hypothesis 3: Self-referred participants are more likely to report changes from baseline to AD control beliefs and susceptibility perceptions after testing than systematically recruited participants, after controlling for *APOE* genotype.

Secondary Hypothesis 4: Self-referred participants are more likely to report changes from baseline to AD concern and worry after testing, as well as stronger negative and positive emotional responses to disclosure, than systematically recruited participants, after controlling for *APOE* genotype.

I tested the aforementioned hypotheses by comparing self-referred and systematically recruited participants in the Risk Evaluation and Education for Alzheimer Disease (REVEAL) Study. In this paper, I first examine associations between referral cohorts and eight behavioral responses: self-reported changes to long-term care insurance, retirement plans, vitamin use, herbal supplement use, mental activities, diet, exercise, and medications. Additionally, I examine the effect of expectations, and then test whether self-referred participants are more likely than systematically recruited participants to report changes in AD susceptibility and controllability perceptions following testing, while confirming whether such differences and changes are correlated with behavioral outcomes. Finally, I examine whether the emotional impact of testing is

stronger for self-referred test recipients than for systematically recruited test recipients, while confirming whether emotional responses are correlated with behavioral outcomes. I then discuss findings from the analyses with an emphasis on their implications for the interpretation of other research and their implications for practice.

METHODS

Overview

This paper summarizes a secondary analysis of data from the second and third trials of the REVEAL Study, a series of multicenter randomized clinical trials examining the psychosocial and behavioral impact of providing AD susceptibility testing with *APOE* genotype disclosure (see Roberts (2011) for a summary of findings). The first REVEAL Study trial (1999-2003) compared the impact of a genetic risk assessment for AD against a risk assessment for AD based on non-genetic factors (i.e., family history and gender), but is excluded from these analyses because of inconsistencies in what constructs were assessed and how they were operationalized relative to the other trials. The second trial (2003-2006) built on work from the first by expanding the participant profile to include more African Americans and by testing a condensed educational and counseling protocol against a traditional model based on genetic testing for cancer susceptibility. The third trial (2006-2009) explored the impact of disclosing that the $\epsilon 4$ allele of *APOE* is associated with coronary artery disease in addition to AD, and also tested a telephone disclosure protocol against in-person disclosure. In each trial, study sites decided individually how to recruit participants. Preliminary analyses of the primary study aims of the second and third trials have been presented elsewhere (Christensen, Roberts, Uhlmann, Whitehouse, Obisesan, Cupples, et al., 2010; Christensen, Roberts,

Uhlmann, Whitehouse, Obisesan, Bhatt, et al., 2010; Green et al., 2006; Roberts et al., 2008) and are being reported separately.

Sites participating in the second trial included the Boston University School of Medicine in Boston, MA; Case Western Reserve Medical School in Cleveland, OH; the Weill School of Medicine in New York, NY; and the Howard University School of Medicine in Washington, DC. The third trial included the same sites, except the University of Michigan School of Public Health in Ann Arbor, MI replaced the Weill School of Medicine.

Procedures

Multidisciplinary teams of experts in the fields of AD, neurology, genetics, genetic counseling, health behavior, psychology, and bioethics created protocols in each trial. An External Advisory Board, as well as institutional review boards at each of the study sites, oversaw development and provided final approval. Participants first completed a baseline assessment that included a telephone interview and self-administered mailed questionnaires. Upon return of the mailed questionnaire, participants received pretest education in one of two forms. A control group in the second REVEAL Study trial had an in-person educational session with a genetic counselor (GC) followed by a separate GC-directed discussion at the time of the blood draw. Experimental groups in the second trial and all participants in the third trial instead received an educational brochure in the mail before a participant-directed question-and-answer at the time of the blood draw. Participants provided informed consent twice during the study: at the point of initial enrollment, and again just before the blood draw for genotyping by a CLIA-certified lab.

Once genotyping was complete, participants received results in one of two forms. All participants in the second trial and a control group in the third trial received results from a GC, physician or health educator in-person. An experimental group in the third trial received results via phone. An overlapping experimental group in the third trial was also told about an association between the $\epsilon 4$ allele of *APOE* and increased risk for cardiovascular disease (CVD). AD risk information included numerical risk assessments through age 85 ranging from 6% to 77% based on their *APOE* genotype, age, gender, self-identified ethnicity, and family history (Christensen et al., 2008; Cupples et al., 2004), as well as “remaining risk” estimates that incorporated their current ages. CVD risk information included the following statement, iterated both verbally and on written summaries: “In addition to Alzheimer’s disease, *APOE* has been found to be connected to heart disease. Some studies have shown that people who carry $\epsilon 4$ also have a higher risk of developing heart disease. Potential strategies to reduce the risk of coronary artery disease associated with $\epsilon 4$ include smoking cessation, a healthy diet, weight loss, treatment of elevated cholesterol, and exercise (with your doctor’s permission).” CVD risk information was reiterated at the end of follow-ups appointments.

Following disclosure, REVEAL researchers followed participants for the period of one year, with a phone call for safety purposes occurring 1 week after disclosure and data collection occurring 6 weeks, 6 months and 12 months after disclosure.

Participants and recruitment

Inclusion criteria varied by REVEAL Study trial. Participants in the second trial were adult first-degree relatives (FDRs) (i.e., child, sibling or parent) of a living or deceased patient with AD. In the third trial, that criterion was relaxed slightly, and

individuals with no affected FDRs were enrolled as well as individuals with a single FDR. Individuals in both trials for whom the average age of onset of AD within the family was 60 years or less were excluded due to the potential that they may be carriers of mutations to other genes (*PS1*, *PS2*, or *APP*) associated with early-onset AD that were not examined in the REVEAL Study. Individuals in both trials with two or more affected FDRs were also excluded from participation because risk models for them could not be developed with sufficient precision. Finally, individuals in the third trial who did not self-identify as either Caucasian or black/African American were excluded at most study sites because of concerns that risk models have questionable validity for other ethnic groups.

Study sites independently decided how to recruit participants. Nearly all sites used a combination of approaches. Active, targeted efforts to enroll individuals with an interest in research or dementia included mailings to participants of research registries, in-person recruitment in the wait areas at neurology clinics, referrals from collaborating physicians, and mailings to individuals who had participated in other AD-related studies. Untargeted efforts included advertisements in local newspapers, flyers posted in clinics, and presentations about the study at community centers. Passive approaches included postings on research-related websites (e.g., clinicaltrials.gov, the Alzheimer's Disease Education and Referral Center), and word-of-mouth. To ensure demographic diversity in the second trial, the study team established a target to enroll roughly equal numbers of adults under the age of 60 and 60 or older. Similarly, the third trial had enrollment quotas by site such that the final sample would have an even proportion of males and females; an even proportion of individuals 60 or older and less than 60 years of age; and $\frac{3}{4}$ would have a single AD-affected FDR while $\frac{1}{4}$ would have no AD-affected FDR. In both trials,

the study team relaxed quotas near the end of the recruitment period to better ensure that overall enrollment numbers would satisfy statistical requirements on primary study hypotheses.

Measures

Referral process

During intake, a research coordinator or research assistant queried participants about how they “heard about the REVEAL Study.” The coordinator or assistant then categorized verbal responses at the time of data collection into response categories, described below. With help from the overall project managers of the second and third trials, I coded these classifications as systematically recruited or self-referred depending on who initiated contact. REVEAL Study personnel initiated contact with systematically recruited participants, whereas self-referred participants initiated contact with the REVEAL Study.

Coded as systematically recruited

1. *From another research study at this hospital (n=77).* Study personnel coordinated with researchers specializing in neurology and Alzheimer’s disease and encouraged them to discuss the REVEAL Study when appropriate. Examples include individuals who completed the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) examining the impact of anti-inflammatory medicines on AD risk (ADAPT Research Group, 2008); and individuals who agreed to donate their brains to AD research centers upon their death.

2. *Someone from the study talked to me in the waiting room (n=6)*. Study personnel approached families in waiting areas of neurology and geriatrics clinics to explain the goals and steps of the research, and to attempt to enroll interested individuals.
3. *Someone from the study called me at home or work (n=22)*. Study personnel cold-called individuals who provided telephone information for research purposes, usually as part of their participation in a research registry.
4. *Alzheimer's Disease Center referral (n=4)*. These individuals contacted the Boston University Alzheimer's Disease Center and either wanted to participate in another study that was closed or for which they did not qualify; or accompanied an AD-affected relative to a research appointment for another study and were invited to participate. In both cases, participants did not have prior knowledge about the REVEAL Study.
5. *Provider referral (n=18)*. These individuals identified a specific nurse, physician, or genetic counselor who provided them information about the REVEAL Study.
6. *Mailing (n=10)*. These individuals responded to a paper-based or electronic mailing sent to them because they had participated in ADAPT, because they were members of the Michigan Alzheimer's Disease Research Center research registry, or because they were a member of the Dementia Coalition in Michigan.

Coded as self-referred

7. *From a brochure or advertisement (n=160)*. The research team created site-specific recruitment brochures and left them in locations where individuals with an interest in AD research might encounter them (e.g., the waiting rooms of neurology clinics). In addition, advertisements in local newspapers or posted flyers in strategic locations (e.g., clinics) provided information about the aims and methods of the study as well

- as a phone number and email address for interested individuals to use to initiate contact with REVEAL Study personnel.
8. *Someone from the study gave a presentation (n=31)*. REVEAL Study personnel presented information about the study during community events about AD and AD research more generally. Study coordinators classified people who approached REVEAL Study personnel at the event and provided intake information or contacted the study afterwards in this category.
 9. *From a friend/family/participant (n=60)*. These individuals learned about the REVEAL Study from an acquaintance (e.g., a friend or co-worker) who was either a participant or had heard about the study another way, usually in the media (e.g., newspaper article, news report), and then initiated contact with a REVEAL Study coordinator.
 10. *Media (n=72)*. These individuals read about the REVEAL Study in a newsletter (e.g., Long Island Alzheimer's Foundation newsletter), newspaper article (e.g., *Ann Arbor News* press release), a book (e.g., *Carved in Sand*), or heard about it at an event (e.g., a Memory Walk) and found information about how to contact the REVEAL Study.
 11. *Self-referred (n=3)*. Study personnel tagged some individuals as "self-referred" without further elaboration.
 12. *Web site (n=51)*. These individuals either i) heard about the study in some unspecified manner and found a website created at one of the participating study sites; ii) visited a news or entertainment website that was discussing the REVEAL Study, such as *USA Today* online; iii) found REVEAL Study details on a website dedicated to helping studies enroll participants (e.g., *clinicaltrials.gov*, the University

- of Michigan ENGAGE website); or iv) said they had learned about the study “online,” “on the internet,” or through a “Google search” without being specific and initiated contact with study personnel.
13. *Health fair (n=1)*. This individual learned about the REVEAL Study by approaching a booth set up at a health fair by study personnel from Howard University.
14. *Wait list from prior trial (n=10)*. Boston University waitlisted individuals who self-referred and wanted to participate in the first REVEAL Study trial but were excluded due to lack of space. Researchers invited them to participate in the second trial.

Primary Outcomes

Advance planning. The 12-month follow up questionnaire asked participants, “Have you made any changes to your long-term care insurance coverage during the past year that were related to the results of your genetic risk assessment?” and “Do you *plan* to make any changes to your long-term care insurance coverage that are related to the results of your genetic risk assessment?” It also asked, “Have you made any changes to your retirement plan during the past year that were related to the results of your genetic risk assessment?” and “Do you *plan* to make any changes to your retirement plan that are related to the results of your genetic risk assessment?” I coded participants ‘1’ if they reported having changed or plans to change a specific plan for the future, ‘0’ otherwise.

Health behaviors. Participants self-reported changes to putative AD prevention behaviors six weeks following results disclosure. Questionnaires in the second trial asked respondents, “Have you made any health or wellness changes to help prevent Alzheimer’s disease?” whereas questionnaires in the third trial asked “Have you made any health or wellness changes?” Participants then reported whether they had changed

specific health behaviors, including diet, exercise, medications, vitamin usage, herbal supplement usage, and mental activities. A second set of items asked participants to indicate whether they planned to make changes to each behavior in the future. I coded participants '1' if they reported having changed or plans to change a specific health behavior, '0' otherwise.

Secondary Outcomes

Prevention discussions. At the end of each AD risk and *APOE* genotype disclosure session, study clinicians indicated on a checklist whether specific topics had been discussed, including “preventative measures.”

AD control. Measures of AD control perceptions differed by REVEAL Study trial. In the second trial, participants rated their agreement on 5-point scales with four statements adapted from the Multidimensional Health Locus of Control Scale (Wallston & Wallston, 1978): “no matter what I do, if I am going to get AD, I will get it,” “if I take care of myself, I can avoid AD,” “there are medicines, foods, or personal behaviors that can reduce severity of AD,” and “if I have a form of a gene that increases my risk for AD, I can take actions that will help prevent it.” In the third trial, participants rated their agreement using the same response options with six statements adapted from the Revised Illness Perceptions Questionnaire (Moss-Morris et al., 2002): “there is a lot the person can do to control his or her symptoms of AD,” “what the person does can determine whether his or her AD gets better or worse,” “the course of the Alzheimer’s disease depends on the person,” “nothing the person does will affect his or her Alzheimer’s disease,” “the person has the power to influence his or her Alzheimer’s disease,” and “the person’s actions will have no effect on the outcome of his/her Alzheimer’s disease.”

Summary measures equaled the mean of responses on scale items (reverse scoring where appropriate), with higher scores representing greater perceived control and scores standardized based on baseline values to permit analyses across trials. Internal consistency of the scale in the second trial was borderline (Cronbach's $\alpha = .65$) but strong in the third trial (Cronbach's $\alpha = .80$).

Perceived AD susceptibility. Questionnaires assessed perceived AD susceptibility in the pre-education mailed questionnaire and in the 6-week follow-up questionnaire using a single item that differed slightly by REVEAL Study trial. In the second trial, participants responded to the question, “on a scale of 0 to 100%, what do you think your chance of developing AD during your lifetime is?” In the third trial, participants responded to the question, “out of 100 people just like you, how many of them do you think will develop Alzheimer’s disease in their lifetime?”

AD concern. A study administrator asked participants at intake to rate their concern about developing AD compared to their concern about other medical problems on 5-point scales ranging from “much less concerned about AD” to “much more concerned about AD;” and the item was repeated in written form on the 6-week follow-up questionnaire.

AD worry. During the phone interview, a study administrator asked participants, “Presently, how often do you think about getting Alzheimer's disease?” Participants responded on a 4-point scale from “not at all/rarely” to “a lot.” The 6-week follow-up questionnaire repeated the item in written form.

Test-specific distress. Two scales in the 6-week follow-up questionnaire assessed distress over susceptibility testing results. The first, the Impact of Event Scale (IES), was

a 15-item self-report scale commonly used in genetics research. It asked participants to rate the frequency of intrusive and avoidance thoughts related to the genetic risk assessment over the past week with response options ranging from 0 (not at all) to 5 (often). Responses were summed to generate a score from 0 to 75, with higher scores indicating greater distress. Internal consistency of this scale was strong (Cronbach's $\alpha=.87$). The second was the 6-item distress subscale of modified version of the Multidimensional Impact of Cancer Risk Assessment (MICRA) Questionnaire (Cella et al., 2002), where participants reported the frequency over the prior week of responses, such as "feeling upset about my test results." Scores on individual items ranged from 0 (never) to 5 (often) and were summed to create a distress score ranging from 0 to 30 where higher scores indicated greater distress. Internal consistency of this scale was also strong (Cronbach's $\alpha=.85$).

Uncertainty. The six-week follow-up questionnaire also included a nine-item subscale of the MICRA that assessed uncertainty about what test results mean and how they can be used. Participants reported the frequency over the prior week of feelings such as, "Being uncertain about what my test results mean about my risk of developing Alzheimer's disease." Scores on individual items ranged from 0 (never) to 5 (often) and were summed to create an uncertainty score ranging from 0 to 45 where higher scores indicated greater uncertainty. Internal consistency of this scale was acceptable (Cronbach's $\alpha=.72$).

Positive experiences. The six-week follow-up questionnaire included a four-item subscale of the MICRA that assessed positive responses to disclosure. Participants reported the frequency over the prior week of feelings such as, "Feeling happy about my

test result.” Scores on individual items ranged from 0 (never) to 5 (often) and were summed to create a score ranging from 0 to 20 where higher scores indicated greater positive experiences. Internal consistency of this scale was acceptable (Cronbach’s $\alpha=.81$).

Other Potential Mediators

Expectations. The baseline written questionnaire asked, “What do you hope to get out of your risk assessment experience?” Participants checked yes/no options that included “reassurance” and “help in decision making.”

Demographics

Participants self-reported age, gender, race, and number of family members with AD at intake and reconfirmed that information during the phone interview or at the blood draw session. Racial groups were classified as “black/African American” and “other” in these analyses because individuals self-identifying as black or African American received one set of AD risk estimates and individuals self-identifying in any other racial category received a separate set of AD risk estimates (note: individuals who self-identified as neither white/Caucasian nor black/African American were excluded from enrollment in the third trial at most sites. See the Participants and Recruitment section for an explanation). In addition, participants self-reported years of education, total household income (response options: <\$10K, \$10-29K, \$30-49K, \$50-69K, \$70-\$99K, \$100K+, refuse to answer), and employment status (full-time, part-time, unemployed, or retired) during the telephone interview. Study records provided information about study site and trial round (second or third trial), as well as *APOE* genotype which was dichotomized

depending on whether a participant carried at least one copy of the *APOE* ϵ 4 allele associated with increased risk for AD or not.

Data analysis

I tested for differences on demographic variables by referral cohort using independent samples t-tests on continuous variables (age and education), 2-proportion tests on race and gender, chi-squared tests on the balance of categorical variables (employment status, ϵ 4 carrier status, trial and randomization arm), and Wilcoxon rank sum tests on skewed or ordinal variables (family history and income, respectively). I used logistic regression to test hypotheses related to behavior changes, changes to AD susceptibility and control perceptions, AD concern and worry; and linear regression to test secondary hypotheses about negative and positive emotional responses to AD risk and *APOE* genotype disclosure. All regression analyses controlled for demographic factors that varied by referral cohort, excluding site. They also controlled for AD worry given prior analyses showing greater AD worry at enrollment among self-referred participants. I conducted all analyses with R version 2.15.0 for Windows (R Development Core Team, 2011).

I used fully conditional specification, also known as multivariate imputation by chained equations, to impute missing values in the data using R package *mice* 2.12 (van Buuren & Groothuis-Oudshoorn, 2011). Models for each imputed variable included the following predictors; referral cohort, outcome variables of focus in this paper, demographic characteristics including genetic knowledge and numeracy, stage of study dropout, AD risk estimates based on genotyping, and *APOE* ϵ 4 status. I ran 20 iterations to create 40 imputed datasets based on recommendations by Azur, et al (2011) and White,

Royston and Wood (2011), and used rules developed by Rubin (1987) to pool estimates and variances from imputed datasets and rules developed by Meng and Rubin (1992) to conduct Wald tests to compare linear regression models and the likelihood ratio test to compare logistic regression models. Item non-response was minimal (≤ 10 instances per item or scale) except for income, for which 22 participants refused to provide; the positive experiences scale, where 23 participants omitted data; and advance planning outcomes assessed at 12 months, where 17 participants were lost to follow up.

RESULTS

Study sample

Table 15 summarizes demographic information for 388 self-referred and 137 systematically recruited participants of the REVEAL Study who received AD risk estimates and *APOE* genotypes. The cohort of self-referred participants was younger, had greater AD worry, was less likely to self-identify as black or African American, had higher household incomes, and was more likely to be employed than the cohort of systematically recruited participants. In addition, the self-referred cohort had a greater percentage of participants from third trial and the Weill School of Medicine and University of Michigan sites than the systematically recruited, which had a greater percentage of participants from the second trial and from the Boston University site.

Seventeen subjects dropped out of the study before the 12-month follow-up, including 12 self-referred and 5 systematically recruited participants (3% and 4% of those cohorts, respectively). Only one of these dropouts occurred prior to the six-week follow-up.

Behavior Changes and Discussions about Prevention

Table 16 and Table 17 show the percentage of participants reporting who made or planned changes to advance planning and health behaviors after the disclosure of test results. Participants tended to be less likely to report changes to long-term care insurance and retirement plans than health behaviors, although only 4% overall reported changes to medications and 6% reported changes to herbal supplements. Plans to change advance planning or health behaviors were more common. Self-referred participants overall were no more likely than systematically recruited participants to report changes or plans to change outcomes of interest, but analyses examining interaction effects found that the association between being $\epsilon 4$ -positive and changing mental activities and diet was stronger within the self-referred cohort than the systematically recruited cohort, as was the association between *APOE* genotype and plans to change long-term care insurance and exercise.

Self-referred participants were not more likely to discuss AD prevention than systematically recruited participants during disclosure sessions, though. Thirty-four percent of the systematically recruited cohort discussed prevention during disclosure sessions compared to 30% of the self-referred cohort ($\chi^2=.74$, $p=.80$). In fact, while nearly identical percentages of self-referred and systematically recruited participants who were $\epsilon 4$ negative discussed prevention strategies (25% and 23%, respectively, $\chi^2=.08$, $p=.39$), trends among $\epsilon 4$ carriers were opposite than anticipated: 38% of the self-referred cohort discussed prevention options compared to 54% of the systematically recruited cohort, $\chi^2=3.73$, $p=.97$ relative to hypotheses).

Pre-test Expectations

A minority of participants expected testing to help in decision making or to provide reassurance. Thirty-six percent of self-referred and 42% of systematically recruited participants expected that testing would help in decision making; and 32% of self-referred and 34% of systematically recruited participants expected testing to provide reassurance. Differences by referral cohort were not significant (decision making: $\chi^2=1.58$, $p=.209$; reassurance: $\chi^2=.09$, $p=.770$).

Participants who expected testing to aid in decision making were more likely to report changes to long-term care insurance, retirement plans, and mental activities by the six week follow-up, but no other outcomes of interest. However, they were more likely to report plans to change nearly all outcomes of interest. See Table 18. Participants who expected testing to provide reassurance reported greater distress (IES: $\Delta=1.78$, 95%CI: .39-3.17, $p=.012$; MICRA distress subscale: $\Delta=.77$, 95%CI: .23-1.30, $p=.005$) and greater uncertainty ($\Delta=1.05$, 95%CI: .14-1.96, $p=.023$) after controlling for *APOE* genotype, with no differences noted on positive experiences, nor changes from baseline to concern or worry. Tests of interaction effects showed that the associations between expectations and emotional responses were not contingent upon *APOE* genotypes.

Changes to Susceptibility and Control Perceptions

Self-referred participants were not more likely to change susceptibility perceptions than systematically recruited participants. Overall, 55% of self-referred participants and 58% of systematically recruited participants reported changes to AD susceptibility perceptions of at least 5% (adjusted OR=.93, 95%CI: .61-1.43, $p=.625$). Numeric changes to AD susceptibility varied by $\epsilon 4$ status, but also showed no association

with referral cohort. On average, susceptibility perceptions increased by 7.6% among self-referred $\epsilon 4$ carriers and 3.9% among systematically recruited $\epsilon 4$ carriers, while susceptibility perceptions dropped by 4.6% and 5.6% among non-carriers who were self-referred and systematically recruited, respectively. Differences by referral cohort were not statistically significant, and the association between $\epsilon 4$ status and changes to susceptibility perceptions did not vary by referral cohort. See Figure 8.

Self-referred participants were also no more likely to change control perceptions than systematically recruited participants. Participants rated the controllability of AD as 3.1 (sd=.76) on a 5-point scale in the second trial and 3.2 (sd=.81) on a 5-point scale in the third trial prior to testing. Overall, 57% of self-referred participants and 63% of systematically recruited participants reported changes to AD control perceptions of at least .5 standardized units (adjusted OR=.94, 95% CI: .61-1.47, $p=.600$) at follow-up. Numeric changes to AD control beliefs did not vary by $\epsilon 4$ status, but changes did vary with referral cohort, where self-referred participants reported a decrease of control of .08 units on average compared to a .15 unit increase among systematically recruited participants. Increases in control perceptions among systematically recruited $\epsilon 4$ carriers were driven by participants in the third trial (Δ in third trial = .28, Δ in second trial = .05) while decreases in control perceptions among self-referred who were $\epsilon 4$ -negative were driven by participants in the second trial (Δ in third trial = -.08, Δ in second trial = -.21).

Importantly, susceptibility and control perceptions at 6 weeks alone were stronger predictors of behavior change than changes to those perceptions from baseline. Table 19 shows the bivariate correlation between changes in perceived AD susceptibility and changes or plans to change long-term care insurance, but no associations with other

behavioral outcomes of interest in this paper. However, absolute perceived susceptibility, as reported at 6 weeks, was correlated strongly with the likelihood of reporting changes or plans to change all behaviors after controlling for change scores.

Affective Responses

Hypothesized changes to concern and worry were only partially supported by data. Figure 9 shows concern and worry scores before and after disclosure of test results. On average, each self-referred participant's concern score was .63 lower after disclosure than before, while systematically recruited participants' concern scores were .72 lower after disclosure than before ($t=.82$, $p=.41$). Contrary to expectations, AD concern scores changed more often among systematically recruited participants (66.8%) than self-referred participants (62.5%), although differences were not statistically significant ($t=-.67$, $p=.748$). Worry scores were .32 lower on average after disclosure than before among self-referred participants, compared to .15 lower among systematically recruited participants; and 47.3% of self-referred participants reported changes to worry, compared to 39.4% of systematically recruited participants ($t=1.43$, $p=.077$). Of note, numerical worry scores decreased more among self-referred participants than systematically recruited participant, but such differences may be attributable to a combination of higher worry among the self-referred cohort prior to testing ($\Delta=.16$, 95%CI: .00-.32, $p=.046$), and floor effects (32% of systematically recruited participants reported the lowest-possible value of worry at baseline, compared to 20% of self-referred participants).

Distress, uncertainty, and positive experiences generally did not vary by referral cohort. As shown in Figure 10 negative emotional responses were stronger among $\epsilon 4$ carriers than non-carriers, and positive experiences were stronger among non-carriers

than carriers, but self-referred participants did not differ from systematically recruited participants on distress or positive responses. However, although uncertainty scores did not differ overall by referral cohort, the association between $\epsilon 4$ status and uncertainty scores was evident only among self-referred participants.

Importantly, not all emotional factors examined here showed associations with behavioral outcomes. Table 20 shows the association between affective responses to disclosure and changes to outcomes of interest. No emotional responses were associated with changes to advance planning by the six-week follow-up, and changes in worry and positive experiences showed few associations with changes to health behaviors. Nearly all emotional factors were associated with changes to vitamin use and mental activities, though; and with the exception of worry, emotional responses were frequently associated with plans to change advance planning and health behaviors.

DISCUSSION

These are some of the first analyses to examine whether individuals who self-refer to genetic susceptibility testing respond different behaviorally than individuals who are systematically recruited into testing. They show that REVEAL Study participants' responses to $\epsilon 4$ positive test results depends on whether or not they had self-referred to the study, at least with respect to changes to mental activities and diet and on plans to change long-term care insurance and exercise.

Notably, self-referred $\epsilon 4$ carriers were more likely to report changes than systematically recruited $\epsilon 4$ carriers despite being less likely to discuss prevention options during the disclosure session. These findings suggest that self-referred participants enrolled more ready to act on results than systematically recruited participants. Many

systematically recruited participants may not have considered prevention or advance planning at the point of enrollment. In addition, important facilitators of behavior change may be greater among individuals who self-refer to interventions than those who are systematically recruited, including behavioral capability and self-efficacy (Snyder et al., 2008). These facilitators were not assessed in the REVEAL Study, but may be important targets to focus on if genetic susceptibility testing is to be used as a tool for health promotion (Becker & Janz, 1987; Strecher & Kreuter, 1995).

Another potential explanation why self-referred $\epsilon 4$ carriers were more likely to act on results than systematically recruited $\epsilon 4$ carriers may be greater feelings of uncertainty following testing. Among the potential mediators I examined, only uncertainty both varied by referral cohort and was statistically associated with changes to mental activities and diet and plans to change long-term care insurance and exercise. Of note, the uncertainty scale combined items that assessed uncertainty about whether or not AD would develop (e.g., understanding what test results means for AD risk) and uncertainty about how to react to testing (e.g., difficulty making decisions about AD screening or prevention) despite evidence that suggests that different types of uncertainty result in different types of coping responses (Babrow, Kasch, & Ford, 1998; Han, Klein, & Arora, 2011; Kasper, Geiger, Freiberger, & Schmidt, 2008). More nuanced measurement of uncertainty following testing may help to reconcile the counterintuitive finding that participants who reported less certainty about how to use test results were more likely to report changes to advance planning and health behaviors.

The findings from these analyses have important implications for the disclosure of genetic information. Given trends in genetic sequencing speeds and costs, individuals are

likely to soon have greater access to their genomic profiles and associated susceptibility information. Whether this information is proffered to patients by clinicians (akin to systematic recruitment) or whether patients will be able to access it only if they proactively request it (akin to self-referral) is a topic of much discussion (Berg, Khoury, & Evans, 2011). The data here suggest that disclosing AD risk and *APOE* genotype information to individuals who demonstrate no prior interest in it is unlikely in and of itself to motivate them to adopt protective health behaviors or change advance planning.

In addition, the analyses presented here highlight the challenges of using genetic testing to promote health behavior changes. The REVEAL Study has been one of few studies that show evidence that genetic testing can motivate any changes to behaviors other than screening; yet, these analyses suggest that only the subset of self-referred participants use testing to inform such changes. The data do suggest that genetic susceptibility testing is useful to those who are ready for it. In addition, more innovative approaches to communicating genetic risk information that target families or are sensitive to biological mechanisms that facilitate or inhibit behaviors may improve the ability of genetic testing to be an effective health promotion tool (McBride, Bryan, Bray, Swan, & Green, 2012; McBride et al., 2010). Until then, practitioners must be sensitive to the potential for studies of genetic susceptibility testing to inflate its ability to change health behavior changes by enrolling self-referred populations.

A number of important findings that were not specific to the question of referral cohort merit discussion here. First, data supported the underlying conceptual model, one that highlights the importance of disease-specific cognitions (i.e., perceived susceptibility, perceived control) and emotional responses to test information. AD

susceptibility, AD concern, distress, and uncertainty after testing were both greater among $\epsilon 4$ carriers than non-carriers, and were associated with behavioral outcomes of interest. Analyses to date have focused on the impact of *APOE* genotype, largely ignoring the psychosocial factors that may mediate any associations with behavioral responses (Chao et al., 2008; Taylor et al., 2010; Vernarelli et al., 2010; Zick et al., 2005). An improved understanding of the psychosocial mechanisms of behavior change may help providers improve risk communication strategies in ways that increase the likelihood of positive behavior changes. In particular, the association between emotional responses and behavior change was strong and consistent. Capitalizing on negative emotions to motivate behavior change requires skill to ensure individuals don't adopt avoidance maladaptive behaviors (Witte, 1992). Consistent evidence showing that negative emotional responses to testing are short-lived (Green et al., 2009; Heshka, Palleschi, Howley, Wilson, & Wells, 2008; Rew, Kaur, McMillan, Mackert, & Bonevac, 2010) may encourage practitioners to focus more attention on empowering behavior change and less attention trying to minimize anxiety and distress.

Second, data showed that susceptibility and control perceptions six weeks after testing were more important determinants of outcomes than changes in those perceptions from baseline. One might expect individuals to change future plans or modify health behaviors in response to genetic test results only if perceptions had changed, as individuals already perceiving a strong risk for AD would presumably already be taking preventive measures. The counterintuitive findings from the analyses reported here may reflect differences in the certainty of information. Baseline perceptions about AD susceptibility and control were uninformed by prior education for many participants, and

may simply reflect guesses. In contrast, post-test perceptions were informed by information provided both during pre-test education and during risk disclosure sessions. *APOE* genetic susceptibility testing does not provide yes/no answers about whether or not a person will develop AD in the future, but it may resolve risk ambiguity and may provide a more scientific basis for rating perceptions about control. If so, it is sensible that individuals were more likely to act on post-test perceptions rather than changes from baseline. Alternatively, testing may have been a “cue to action” that finally prompted individuals to initiate changes to health behavior and advance planning.

Third, the expectations individuals held at enrollment were associated with responses to testing. Although unassociated with referral cohort, individuals who expected that testing would help in decision making were more likely to make changes to advance planning and to plan health behavior changes than those who expected otherwise. Interestingly, the impact of expectations about decision making on outcomes was unassociated with *APOE* genotype, suggesting that individuals were primed to act regardless of their genetic risk for AD. Ironically, individuals who expected that testing would provide reassurance reported stronger negative emotional responses after testing, even if they were not at increased genetic risk for AD. The tendency to underestimate distress following disclosure of results indicating no increased risk has been observed in other contexts (e.g., HIV testing (Sieff, Dawes, & Loewenstein, 1999)), although the strong tendency is for people to overestimate negative emotional responses to medical information (Damschroder, Zikmund-Fisher, & Ubel, 2005; Ditto, Hawkins, & Pizarro, 2005; Dolders, Zeegers, Groot, & Ament, 2006; Fried et al., 2006; Riis, Loewenstein, Baron, & Jepson, 2005). It is possible that participants expecting an emotional response

were more attentive to ‘negative’ information, with $\epsilon 4$ carriers focusing on their increased AD risk and non-carriers focusing on the fact that they still had AD risk, particularly if they had a family history of the condition. Alternatively, they may have expected to feel reassured through the resolution of uncertainty, and found scripted disclosure messages that risk estimates were “based on our current knowledge” and subject to change particularly unsettling,

Lastly, the analyses provide rare insight into positive emotional responses to genetic susceptibility information. As might be expected, individuals who were told they were not carriers of a risk-increasing form of *APOE* reported a stronger positive experience to testing than $\epsilon 4$ carriers. Unlike distress, concern and uncertainty, however, positive experiences were not associated with behavioral outcomes. Few health behavior theories incorporate positive emotions as key determinants, and our data does not suggest that they are. While practitioners may strive for individuals to have ‘good’ testing experiences, the implications for health behaviors and future planning appear to be minimal.

Limitations

Some important limitations must be noted. The analyses in this paper compare self-referral strategies against systematic recruitment with a focus on process, but differences in sampling frames complicate the interpretation of results. In particular, differences between the self-referred and systematically recruited cohort may be understated because much of the systematically recruited cohort was drawn from individuals who had participated in other AD research. These individuals may not have had prior knowledge about genetic susceptibility testing specifically, but are likely to

have had a stronger interest in AD prevention and AD research than individuals who might normally be expected to enroll through population-based recruitment methods (e.g., the population at-large or patient populations from a specific practice). Second, many outcomes of interest were single-item self-reports of behavior change and therefore of questionable validity and subject to biases introduced by social desirability (Schwarz, 1994). Unlike interventions where individuals are systematically recruited in the hopes that they will adopt behaviors that they *should* do but may not want to do, AD has no proven prevention strategies, meaning many systematically recruited individuals were being asked to participate in an intervention that had no clear utility for them. Finally, study participants, whether self-referred or systematically recruited, were still self-selected and unrepresentative of the general population overall on important demographic factors such as education and income.

TABLES

Table 15. Descriptive statistics of REVEAL Study participants who received genetic risk assessments.

| | Systematically Recruited (n=137) | Self-Referred (n=388) | Total (n=525) | p |
|--|----------------------------------|-----------------------|---------------|-----------------|
| <i>Continuous/ordinal variables: mean (sd)</i> | | | | |
| Age in years | 61.7 (11.8) | 57.0 (11.4) | 58.2 (11.7) | <.001 |
| Years of education | 16.2 (2.8) | 16.5 (2.3) | 16.5 (2.5) | .227 |
| # of affected relatives | 1.6 (1.2) | 1.8 (1.3) | 1.7 (1.2) | .094 |
| Median income | \$50-69K | \$70-99K | \$70-99K | .007 |
| AD worry | 2.1 (.8) | 1.9 (.7) | 2.1 (.8) | <.001 |
| <i>Categorical variables: n (%)</i> | | | | |
| Black/African American | 40 (29.2%) | 45 (11.6%) | 85 (16.2%) | <.001 |
| Male | 53 (38.7%) | 140 (36.1%) | 193 (36.8%) | .660 |
| Employed part/full time | 73 (53.3%) | 260 (67.0%) | 333 (63.4%) | .006 |
| ε4 carrier | 46 (33.6%) | 144 (37.1%) | 190 (36.2%) | .524 |
| Site by referral cohort | | | | <.001 |
| Boston University | 63 (46%) | 95 (24.5%) | 158 (30.1%) | |
| Case Western Reserve | 31 (22.6%) | 94 (24.2%) | 125 (23.8%) | |
| Howard University | 29 (21.2%) | 62 (16.0%) | 91 (17.3%) | |
| Weill School of Medicine | 9 (6.6%) | 74 (19.1%) | 83 (15.8%) | |
| University of Michigan | 5 (3.6%) | 63 (16.2%) | 68 (13.0%) | |
| Trial by referral cohort | | | | .007 |
| 2 nd Trial | 85 (62.0%) | 187 (48.2%) | 272 (51.8%) | |
| 3 rd Trial | 52 (38.0%) | 201 (51.8%) | 253 (48.2%) | |
| Randomization arm by trial and referral cohort | | | | |
| 2 nd Trial | | | | .408 |
| Extended Protocol | 24 (28.2%) | 66 (35.3%) | 90 (33.1%) | |
| Condensed Protocol (GC) | 33 (38.8%) | 59 (31.6%) | 92 (33.8%) | |
| Condensed Protocol (MD) | 28 (32.9%) | 62 (33.2%) | 90 (33.1%) | |
| 3 rd Trial | | | | |
| AD+CVD disclosure | 23 (44.2%) | 96 (47.8%) | 119 (47.0%) | .765 |
| Phone disclosure | 19 (36.5%) | 103 (51.2%) | 122 (48.2%) | .083 |

Table 16. Number and percentage of participants reporting changes to advance planning and health behaviors stratified by referral cohort and, in the interaction model, $\epsilon 4$ status. Adjusted odds ratios control for demographic and emotional factors that differed by referral cohort: age, race, income, employment status, study trial, and pretest worry. Numbers reporting changes are not integers because they represent pooled estimates across 40 imputed datasets.

| Changed ... | Main effect model comparing self-referred & systematically recruited cohorts | | | | Interaction model testing whether the association between $\epsilon 4$ status and behavioral outcomes varied by referral cohort | | | | | | |
|-----------------------------|---|------------------------------|----------------------------|-------------|--|---------------------------|----------------------------|--------------------------|--------------------------|----------------------------|-------------|
| | Self- Referred (n=388) | Syst Recruited (n=137) | Adjusted OR (95% CI) | p (add)* | Self-Referred | | | Systematically Recruited | | | |
| | | | | | $\epsilon 4$ - (n=244) | $\epsilon 4$ + (n=144) | Adjusted OR (95% CI) | $\epsilon 4$ - (n=91) | $\epsilon 4$ + (n=46) | Adjusted OR (95% CI) | p (int)† |
| Long-term care insurance | 25.0 (6.4%) | 9.1 (6.6%) | .93 (.40-2.19) | .564 | 10.8 (4.4%) | 14.1 (9.8%) | 2.08 (.89-4.88) | 6.1 (6.6%) | 3.0 (6.5%) | .76 (.17-3.34) | .244 |
| Retirement plans | 26.9 (6.9%) | 8.0 (5.8%) | 1.19 (.49-2.91) | .351 | 13.0 (5.3%) | 13.9 (9.7%) | 1.75 (.78-3.94) | 6.0 (6.5%) | 2.0 (4.3%) | .47 (.09-2.59) | .172 |
| Vitamin use | 54.8 (14.1%) | 16.5 (12.1%) | 1.19 (.63-2.25) | .298 | 25.2 (10.3%) | 29.6 (20.5%) | 1.91 (1.05-3.50) | 9.5 (10.5%) | 7.0 (15.2%) | 1.27 (.43-3.80) | .522 |
| Herbal supplement use | 20.0 (5.2%) | 9.2 (6.7%) | 1.06 (.42-2.69) | .450 | 6.7 (2.7%) | 13.4 (9.3%) | 3.82 (1.28-11.34) | 4.2 (4.6%) | 5.0 (10.9%) | 2.84 (.65-12.40) | .748 |
| Mental activities | 84.0 (21.7%) | 23.6 (17.2%) | 1.52 (.89-2.62) | .064 | 39.4 (16.1%) | 44.7 (31%) | 2.30 (1.37-3.84) | 17.6 (19.3%) | 6.0 (13.0%) | .64 (.23-1.80) | .029 |
| Diet | 74.3 (19.1%) | 22.1 (16.1%) | 1.24 (.71-2.16) | .225 | 35.9 (14.7%) | 38.4 (26.6%) | 1.96 (1.16-3.32) | 17.1 (18.8%) | 5.0 (10.9%) | .50 (.17-1.48) | .026 |
| Exercise | 70 (18.0%) | 22.1 (16.1%) | 1.22 (.70-2.14) | .239 | 35.8 (14.7%) | 34.2 (23.7%) | 1.77 (1.03-3.04) | 12.1 (13.3%) | 10.0 (21.7%) | 2.01 (.78-5.22) | .820 |
| Medications | 16.1 (4.2%) | 3.0 (2.2%) | 2.17 (.59-7.97) | .121 | 7.1 (2.9%) | 9.0 (6.3%) | 2.26 (.80-6.37) | 3.0 (3.3%) | 0 (0%) | NA | .987 |

* One-sided test of the hypothesis that self-referred participants are more likely to report changes.

† Two-sided test of whether the impact of $\epsilon 4$ status on the likelihood of planning to change behaviors differs by referral cohort.

‡ Unable to calculate odds ratio because $\epsilon 4$ -positive systematically recruited participants reported no changes.

Table 17. Number and percentage of participants reporting plans to change advance planning and health behaviors stratified by referral cohort and, in the interaction model, $\epsilon 4$ status. Adjusted odds ratios control for demographic and emotional factors that differed by referral cohort: age, race, income, employment status and study trial. Numbers reporting plans are not integers because they represent pooled estimates across 40 imputed datasets.

| Planned to change... | Main effect model comparing self-referred and systematically recruited participants | | | | Interaction model testing whether the association between $\epsilon 4$ status and behavioral outcomes varied by referral cohort | | | | | | | |
|--------------------------|---|---------------------------|-------------------------|-------------|---|---------------------------|-------------------------|--------------------------|--------------------------|-------------------------|-------------------------|--|
| | Self-Referred (n=388) | Syst Recruited (n=137) | Adjusted OR (95% CI) | p (add)* | Self-Referred | | Adjusted OR (95% CI) | Systematically Recruited | | Adjusted OR (95% CI) | p (int) [†] | |
| | | | | | $\epsilon 4$ - (n=244) | $\epsilon 4$ + (n=144) | | $\epsilon 4$ - (n=91) | $\epsilon 4$ + (n=46) | | | |
| Long-term care insurance | 65.4 (16.9%) | 14.9 (10.9%) | 1.43 (.73-2.79) | .147 | 20.6 (8.4%) | 44.9 (31.2%) | 4.52 (2.47-8.25) | 10.9 (12%) | 4.0 (8.7%) | .48 (.14-1.72) | .002 | |
| Retirement plans | 37.4 (9.6%) | 12.3 (9.0%) | .96 (.45-2.04) | .544 | 12.0 (4.9%) | 25.4 (17.7%) | 3.86 (1.83-8.11) | 5.3 (5.8%) | 7.0 (15.2%) | 2.46 (.70-8.58) | .541 | |
| Vitamin use | 63.7 (16.4%) | 28.6 (20.8%) | .84 (.49-1.44) | .737 | 32.2 (13.2%) | 31.5 (21.9%) | 1.64 (.93-2.91) | 19.6 (21.5%) | 9.0 (19.6%) | .82 (.32-2.09) | .209 | |
| Herbal supplement use | 36.9 (9.5%) | 19.6 (14.3%) | .70 (.36-1.34) | .860 | 18.4 (7.5%) | 18.5 (12.9%) | 1.72 (.83-3.53) | 11.6 (12.7%) | 8.0 (17.4%) | 1.47 (.52-4.18) | .808 | |
| Mental activities | 133.5 (34.4%) | 45.9 (33.5%) | 1.07 (.69-1.68) | .377 | 83.0 (34%) | 50.5 (35.1%) | .94 (.60-1.47) | 33.9 (37.2%) | 12.0 (26.1%) | .53 (.24-1.20) | .227 | |
| Diet | 123.3 (31.8%) | 34.3 (25%) | 1.32 (.82-2.13) | .129 | 75.0 (30.7%) | 48.3 (33.5%) | 1.10 (.69-1.74) | 24.3 (26.7%) | 10.0 (21.7%) | .67 (.28-1.62) | .331 | |
| Exercise | 141.2 (36.4%) | 40.4 (29.5%) | 1.15 (.73-1.82) | .272 | 85.8 (35.2%) | 55.4 (38.5%) | 1.10 (.70-1.71) | 31.4 (34.5%) | 9.0 (19.6%) | .38 (.16-.92) | .035 | |
| Medications | 25.4 (6.5%) | 12.1 (8.8%) | .67 (.31-1.45) | .848 | 13.3 (5.5%) | 12.1 (8.4%) | 1.48 (.64-3.42) | 8.1 (8.9%) | 4.0 (8.7%) | .84 (.23-3.10) | .476 | |

* One-sided test of the hypothesis that self-referred participants are more likely to plan changes.

[†] Two-sided test of whether the impact of $\epsilon 4$ status on the likelihood of planning to change behaviors differs by referral cohort.

Table 18. Results from logistic regression models examining whether individuals who enrolled expecting testing to aid in decision making were more likely to report changes to advance planning or health behaviors after testing. Models control for disclosed *APOE* genotype. Interactions between *APOE* genotype and pretest expectations are not reported here due to a lack of statistically significant findings.

| Outcome | Model 1: Changed outcome | | Model 2: Plan to change outcome | |
|--------------------------|-----------------------------|-------------|------------------------------------|-----------------|
| | OR (95% CI) | p | OR (95% CI) | p |
| Long-term care insurance | 2.53 (1.23-5.21) | .012 | 1.79 (1.09-2.93) | .022 |
| Retirement plans | 2.36 (1.17-4.75) | .016 | 2.95 (1.58-5.51) | .001 |
| Vitamins | 1.54 (.92-2.57) | .102 | 1.46 (.92-2.32) | .112 |
| Herbal supplements | 1.20 (.54-2.63) | .655 | 1.88 (1.07-3.31) | .029 |
| Mental activities | 1.62 (1.05-2.51) | .030 | 2.11 (1.45-3.07) | <.001 |
| Diet | 1.28 (.81-2.01) | .292 | 1.63 (1.11-2.40) | .012 |
| Exercise | 1.32 (.83-2.11) | .236 | 1.42 (.98-2.07) | .063 |
| Medications | .76 (.28-2.05) | .594 | 1.79 (1.09-2.93) | .022 |

Table 19. Bivariate associations between outcomes of interest and AD susceptibility perceptions, susceptibility perceptions 6 weeks after results disclosure, changes to control perceptions, and control perceptions 6 weeks after disclosure. Odds ratios refer to the increase in the likelihood of reporting a change or plan to change behavior per 10% increase in perceived susceptibility to AD or a 1 standard deviation increase in control perceptions. The top half of the table reports on changes to outcomes reported by six weeks, whereas the bottom half of the table reports on plans to change outcomes of interest.

| <i>Changed...</i> | Change in perceived susceptibility | | Perceived susceptibility at 6 weeks | | Change in perceived control | | Perceived control at 6 weeks | |
|-----------------------------|------------------------------------|-------------|-------------------------------------|-----------------|-----------------------------|------|------------------------------|-----------------|
| | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| LTC insurance | 1.16 (1.01-1.34) | .036 | 1.22 (1.07-1.41) | .004 | .86 (.59-1.25) | .435 | 1.00 (.72-1.40) | .983 |
| Retirement plans | 1.07 (.92-1.23) | .375 | 1.02 (.88-1.18) | .777 | 1.06 (.74-1.53) | .749 | 1.32 (.86-1.68) | .273 |
| Vitamins | 1.03 (.93-1.15) | .573 | 1.23 (1.11-1.36) | <.001 | .95 (.72-1.24) | .700 | 1.13 (.89-1.45) | .315 |
| Herbal supps | 1.11 (.95-1.30) | .187 | 1.22 (1.05-1.42) | .009 | 1.01 (.67-1.51) | .967 | 1.69 (1.12-2.56) | .013 |
| Mental activities | 1.11 (1.02-1.22) | .022 | 1.22 (1.11-1.33) | <.001 | 1.05 (.83-1.32) | .687 | 1.27 (1.03-1.57) | .027 |
| Diet | 1.06 (.96-1.16) | .240 | 1.09 (1.00-1.20) | .055 | 1.10 (.87-1.39) | .445 | 1.41 (1.13-1.77) | .002 |
| Exercise | 1.11 (1.01-1.22) | .032 | 1.13 (1.03-1.24) | .010 | 1.11 (.88-1.41) | .376 | 1.26 (1.01-1.57) | .043 |
| Medications | 1.08 (.89-1.31) | .432 | 1.10 (.91-1.32) | .322 | 1.04 (.64-1.68) | .876 | 1.81 (1.11-2.95) | .017 |
| <i>Planned to change...</i> | | | | | | | | |
| LTC insurance | 1.11 (1.01-1.23) | .038 | 1.15 (1.05-1.27) | .004 | 1.15 (.89-1.48) | .281 | 1.13 (.90-1.43) | .286 |
| Retirement plans | 1.12 (1.00-1.27) | .060 | 1.21 (1.08-1.36) | .001 | .89 (.65-1.21) | .456 | 1.10 (.83-1.46) | .499 |
| Vitamins | 1.06 (.96-1.17) | .225 | 1.21 (1.10-1.32) | <.001 | .86 (.67-1.10) | .227 | 1.26 (1.01-1.58) | .044 |
| Herbal supps | 1.15 (1.03-1.29) | .017 | 1.20 (1.08-1.35) | .001 | .83 (.61-1.13) | .233 | 1.27 (.96-1.69) | .098 |
| Mental activities | 1.00 (.93-1.08) | .986 | 1.07 (.99-1.16) | .072 | .85 (.70-1.03) | .105 | 1.32 (1.11-1.58) | .002 |
| Diet | 1.04 (.96-1.13) | .282 | 1.03 (.95-1.12) | .454 | .98 (.80-1.19) | .811 | 1.42 (1.17-1.72) | <.001 |
| Exercise | 1.07 (.99-1.16) | .083 | 1.02 (.95-1.11) | .537 | 1.02 (.84-1.23) | .870 | 1.51 (1.26-1.82) | <.001 |
| Medications | 1.04 (.90-1.20) | .570 | 1.33 (1.17-1.51) | <.001 | .87 (.61-1.24) | .430 | 1.32 (.95-1.85) | .098 |

Table 20. Bivariate associations between emotional responses to testing and changes or plans to change outcomes of interest, as examined using logistic regression. Figures refer to the increase in odds of reporting a change to a specific behavior per standardized-unit increase from baseline for concern and worry; and per standardized-unit increase in distress, uncertainty, and positive experiences reported six weeks after disclosure of results. The top half of the table reports on changes to outcomes reported by six weeks, whereas the bottom half of the table reports on plans to change outcomes of interest.

| <i>Changed ...</i> | Δ to Concern | Δ in Worry | Distress (IES) | Distress (MICRA) | Uncertainty | Positive experiences |
|------------------------------|------------------------|----------------------|---------------------|---------------------|---------------------|-------------------------|
| LTC insurance | 1.42 | 1.08 | 1.09 | 1.08 | .96 | 1.19 |
| Retirement plans | 1.02 | .90 | 1.18 | 1.13 | 1.18 | .86 |
| Vitamins | 1.35 ^(a) | 1.36 ^(a) | 1.47 ^(c) | 1.31 ^(b) | 1.47 ^(c) | .92 |
| Herbal supplements | 1.27 | 1.23 | 1.33 | 1.34 ^(a) | 1.33 | 1.13 |
| Mental activities | 1.37 ^(b) | 1.24 | 1.50 ^(c) | 1.53 ^(c) | 1.61 ^(c) | .79 ^(a) |
| Diet | 1.20 | 1.18 | 1.15 | 1.29 ^(b) | 1.26 ^(a) | .86 |
| Exercise | 1.11 | 1.16 | 1.24 ^(a) | 1.18 | 1.22 | .91 |
| Medications | 1.41 | 1.34 | 1.39 ^(a) | 1.09 | 1.47 ^(a) | .67 |
| <i>Planned to change ...</i> | | | | | | |
| LTC insurance | 1.31 ^(a) | 1.25 | 1.37 ^(b) | 1.40 ^(c) | 1.43 ^(c) | .92 |
| Retirement plans | 1.20 | 1.15 | 1.45 ^(c) | 1.37 ^(b) | 1.40 ^(b) | 1.01 |
| Vitamins | 1.29 ^(a) | 1.27 | 1.40 ^(c) | 1.41 ^(c) | 1.48 ^(c) | .85 |
| Herbal supplements | 1.64 ^(b) | .98 | 1.28 ^(a) | 1.36 ^(b) | 1.36 ^(a) | 1.12 |
| Mental activities | 1.16 | 1.15 | 1.56 ^(c) | 1.41 ^(c) | 1.65 ^(c) | .74 ^(b) |
| Diet | .99 | 1.03 | 1.24 ^(a) | 1.21 ^(a) | 1.36 ^(b) | .79 ^(a) |
| Exercise | 1.09 | .99 | 1.23 ^(a) | 1.16 | 1.30 ^(b) | .78 ^(a) |
| Medications | 1.18 | .99 | 1.03 | 1.42 ^(b) | 1.53 ^(b) | 1.24 |

(a) $p < .05$

(b) $p < .01$

(c) $p < .001$

FIGURES

Figure 7. Conceptual model tested in Chapter 6.

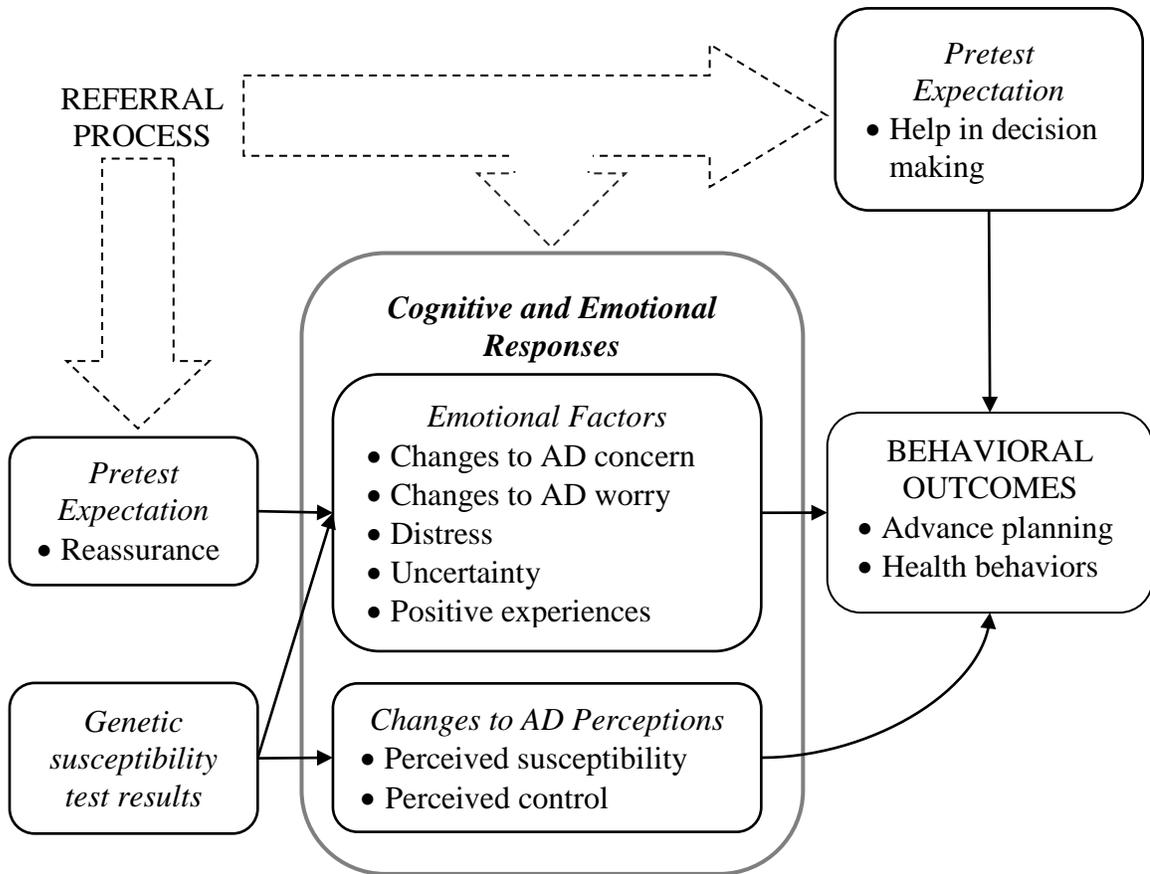


Figure 8. AD susceptibility and control perceptions at baseline and 6 weeks after disclosure of test results, stratified by referral cohort and $\epsilon 4$ status. β estimates refer to the difference in change from baseline among $\epsilon 4$ carriers compared to non-carriers ($\epsilon 4$ status) and the difference in change from baseline among self-referred participants compared to systematically recruited participants (referral status). “Interaction” refers to a test of interaction between $\epsilon 4$ status and referral cohort. Analyses adjust for demographic factors and emotional factors that varied by referral cohort at baseline: age, race, income, employment status, study trial, and AD worry.

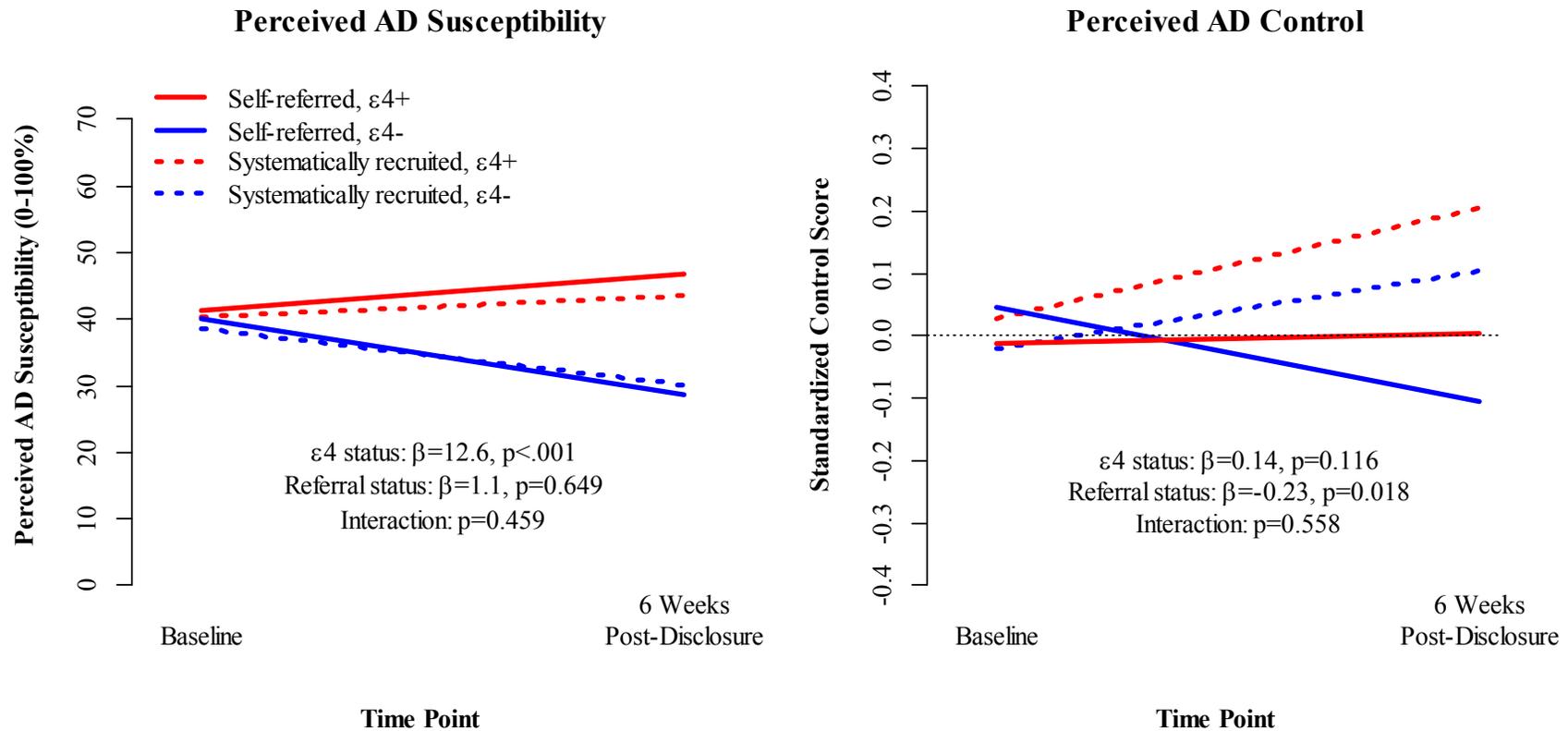


Figure 9. Perceived AD concern and worry before and after testing, stratified by referral cohort and $\epsilon 4$ status. β estimates refer to the difference in change from baseline among $\epsilon 4$ carriers compared to non-carriers ($\epsilon 4$ status) and the difference in change from baseline among self-referred participants compared to systematically recruited participants (referral status). “Interaction” refers to a test of interaction between $\epsilon 4$ status and referral cohort. Analyses adjust for demographic and emotional factors that varied by referral cohort at baseline: age, race, income, employment status, study trial and AD worry.

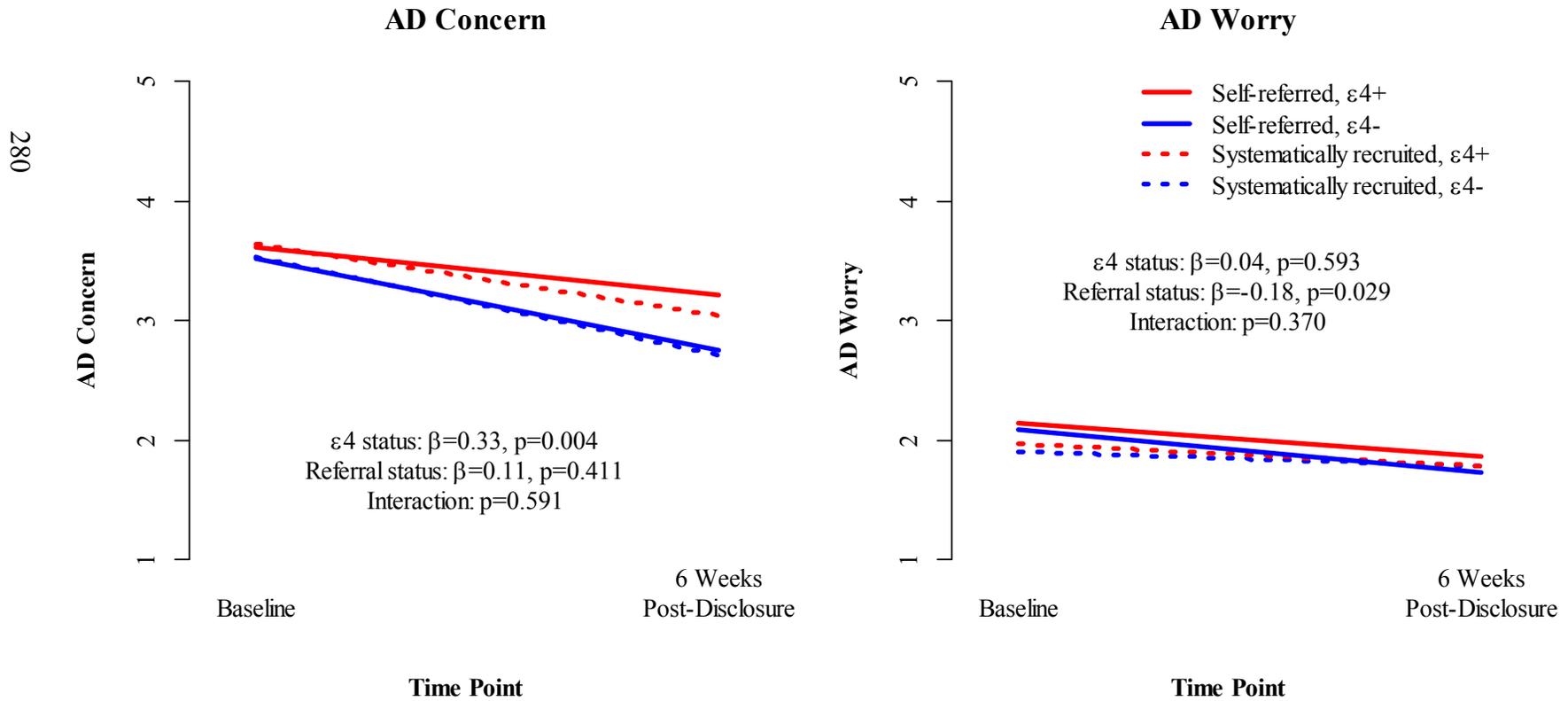
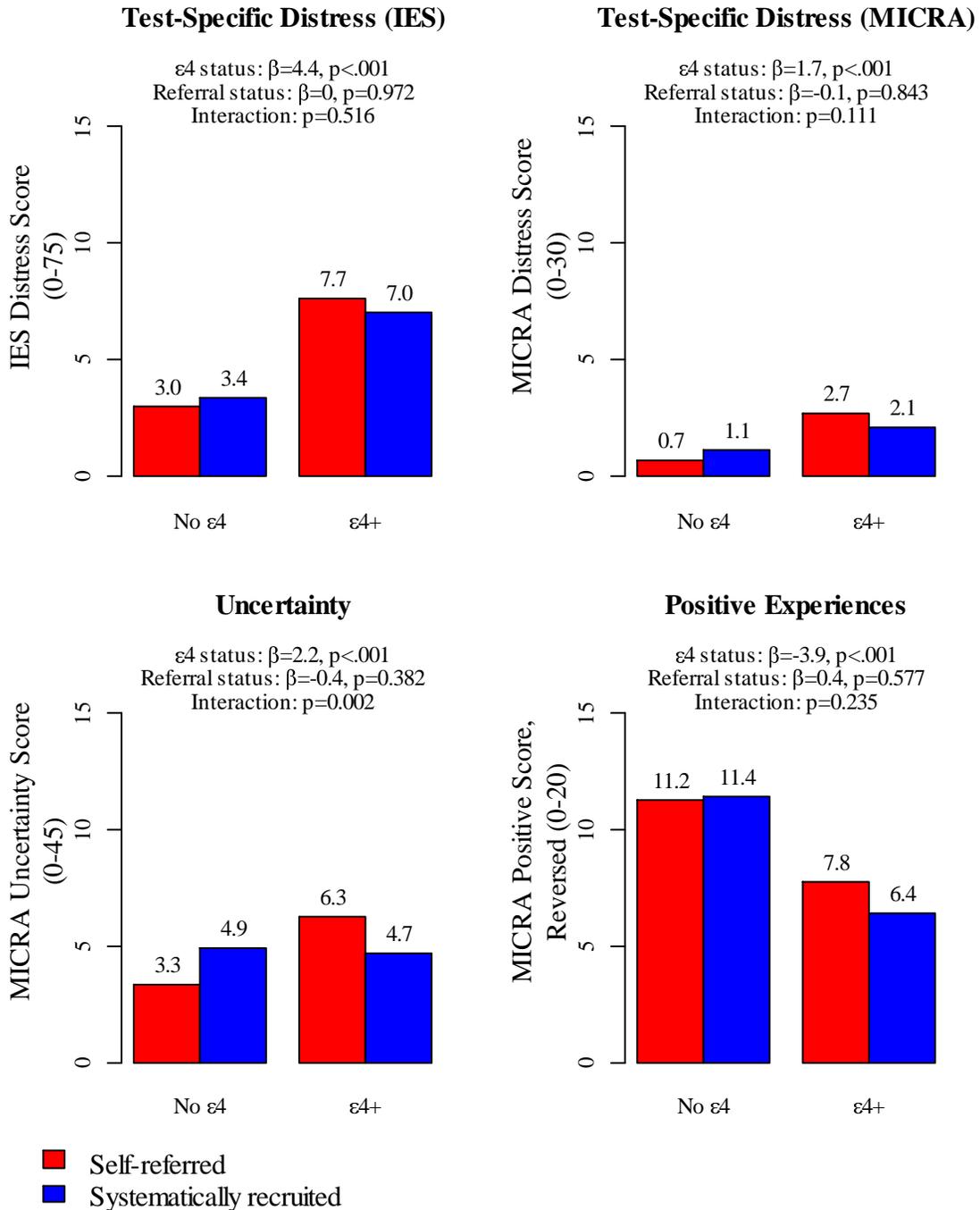


Figure 10. Distress, uncertainty, and positive responses six weeks after testing, stratified by referral cohort and $\epsilon 4$ status. β estimates refer to main effect difference between $\epsilon 4$ carriers and non-carriers ($\epsilon 4$ status), and the difference between self-referred participants and systematically recruited participants (referral status). “Interaction” refers to a test of interaction between $\epsilon 4$ status and referral cohort. Analyses adjust for demographic and emotional factors that varied by referral cohort at baseline: age, race, income, employment status, study trial, and AD worry.



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CHAPTER 7

CONCLUSIONS

The overall goal of this dissertation was to understand the implications of enrolling self-referred populations in genetic susceptibility testing research. Using data from the REVEAL Study, I compared self-referred and systematically recruited participants in a series of secondary data analyses that examined demographic and psychosocial differences at enrollment, disparities in test uptake, and differential responses to test results. I summarize the findings from each analysis here.

SUMMARY OF RESULTS

In Paper 1, I explored how self-referral enrolled a different population of participants into genetic susceptibility testing for AD than systematic recruitment. I examined demographic factors, finding that the self-referred cohort was younger and had a lower percentage of African Americans than the systematically recruited cohort. It also had participants with higher household incomes and stronger family histories of AD, and likely would have had a greater percentage of women than the systematically recruited cohort had gender quotas not been instituted. I also compared cohorts on cognitive factors frequently associated with uptake of testing and health behavior changes, finding greater interest among self-referred participants. However, I found no differences on AD illness

perceptions (i.e., perceived susceptibility, perceived seriousness, genetic or lifestyle causal beliefs, or control beliefs), beliefs about testing (perceived benefits and perceived risks and limitations), or self-efficacy about testing. Lastly, I tested whether the cohorts differed on emotional factors, finding the self-referred cohort to have greater worry and marginally greater concern about AD than the systematically recruited cohort.

In Paper 2, I tested whether the self-referred cohort was more likely to follow through with testing than the systematically recruited cohort following education. I found that systematically recruited participants were more likely to drop out at the earliest phases of the study. However, analyses restricted to the study population that was offered pretest education showed that self-referred participants were no more likely to follow through with testing than systematically recruited participants. I also examined how self-referred participants responded to pre-test information, finding that they were no more likely than systematically recruited participants to change AD susceptibility perceptions following education, but also finding that they were more likely to correct a lack of understanding about whether testing could provide definitive answers about AD risk.

In Paper 3, I examined whether self-referred participants were more likely to report changes to advance planning or health behaviors than systematically recruited participants in response to testing. Findings suggested that self-referred participants were more likely to make or plan changes to long-term care insurance, mental activities, diet and exercise in response to learning they had an increased genetic risk for AD. I also explored potential mechanisms that might explain any differences, and found that feelings of uncertainty following testing both varied by referral cohort and predicted changes or plans to change those outcomes of interest.

Each paper also reported a number of important ancillary findings. Paper 1 highlighted that systematically recruited participants were still self-selected and unrepresentative of the population at large, at least with respect to educational attainment and household income. Paper 1 also emphasized how individuals who seek to learn more about genetic susceptibility testing for AD are overwhelmingly interested in testing and tend to overestimate their susceptibility to AD, while rating heredity as a stronger determinant of AD risk than lifestyle. At the same time, they judge the benefits of testing to far outweigh its risks and limitations, and they have strong confidence in their ability to cope with learning that they might be at increased genetic risk for disease.

Ancillary findings on Paper 2 related to factors that were associated with study dropout after education but before disclosure of test results. Demographically, women, African Americans, participants with less education or lower household incomes, and participants who were not employed were more likely to drop out between the offer of education and before results disclosure than their counterparts. Cognitive factors that predicted dropout included perceptions of greater risks and limitations to testing and lower coping self-efficacy, and emotional predictors of dropout included greater AD concern.

Ancillary findings on Paper 3 related to factors that affected the likelihood of making or planning changes to advance planning and health behaviors. In addition to being more likely to report changes to vitamin and herbal supplement usage, as reported in other papers (Chao et al., 2008; Vernarelli et al., 2010), self-referred $\epsilon 4$ carriers were more likely than non-carriers to report changes to mental activities and diet. They were also more likely to report plans to change long-term care insurance, as noted by Zick et

al. (2005) and Taylor et al. (2010), and retirement plans. Psychosocial factors that predicted changes included post-test AD susceptibility and control perceptions, pretest expectations that testing would aid in decision making, test-specific distress and post-test uncertainty.

Two important themes emerged across studies:

1. *Self-referred participants in AD genetic susceptibility testing research process information differently than systematically recruited participants*

The demographic profile of self-referred participants in the REVEAL Study differed from that of systematically recruited participants in ways that are similar to other studies comparing the two referral processes (DeBar et al., 2009; Henrikson, Harris, & Bowen, 2007; Snyder et al., 2008). Furthermore, this dissertation showed differences in study dropout common to other studies comparing self-referred and systematically recruited participants (McBride et al., 1998). What this dissertation adds to the literature is evidence that self-referred participants are more responsive to pretest education and disclosure of genetic test results than systematically recruited participants. Self-referred participants were more likely to internalize educational messages that *APOE* testing does not provide definitive information about future AD onset, and self-referred participants were more responsive to learning that they were $\epsilon 4$ carriers with respect to making or planning changes to advance planning and health behaviors than systematically recruited participants.

Unfortunately, the findings from this dissertation provide minimal insight about why differences in responses to education and disclosure were observed. Cohort differences on testing beliefs, illness perceptions, and behavioral beliefs were not evident.

The potential exists that the process of self-referral affected how individuals responded to the information provided during education and results disclosure. Self Determination Theory suggests that situations promoting autonomy, like self-referral, increase intrinsic motivation (Ryan & Deci, 2000). Recruitment methods that facilitate self-referral may encourage participants to be proactive about engaging with educational materials and initiating behavior change. Systematic recruitment, on the other hand, may set a precedent that encourages participants to be more responsive rather than proactive during the experience of testing. This argument is highly speculative, particularly because it would suggest that self-referred participants would be more likely than systematically recruited participants to make or plan changes to advance planning or health behaviors *regardless* of *APOE* genotype. Nevertheless, the potential exists that the process of self-referral itself explains some differences between referral cohorts.

A more promising explanation is that self-referred participants process AD risk information with different motivations than systematically recruited participants. While some theoretical perspectives such as the Elaboration Likelihood Model suggest that emotional arousal can distract individuals and make them less attentive to information (Petty & Cacioppo, 1986), the motivated reasoning perspective suggests that aroused individuals will attend to information in ways that are consistent with existing goals (Kunda, 1990; Liberman & Chaiken, 1992). Despite messages that AD risk is largely non-modifiable, REVEAL Study participants rated gaining information about prevention as the most important reason for seeking AD genetic susceptibility testing (Christensen, Roberts, Uhlmann, & Green, 2011). If reducing the threat of AD was a more important goal to self-referred participants than systematically recruited participants, they may have

been more receptive to messages consistent with that goal. Defensive reasoning, where individuals process messages in ways that minimize a threat (Chaiken, Giner-Sorolla, & Chen, 1996), may be a particularly viable explanation why self-referred participants were both more likely to recognize that *APOE* testing is not deterministic and additionally believe that modifications to health behaviors can reduce AD threats, particularly if they are found to be at increased genetic risk. Some REVEAL Study findings run counter to the defensive processing perspective: $\epsilon 4$ carriers in the second REVEAL Study trial were more likely to recall results than non-carriers (Eckert et al., 2006), whereas the defensive reasoning perspective would argue that they would be more likely to forget such results. Future work will need to explore differences in the way self-referred and systematically recruited individuals process information in more detail.

2. *Emotions are important determinants of uptake and behavioral responses to genetic susceptibility testing for AD.*

Many studies of genetic susceptibility testing have examined negative emotional responses, such as anxiety, depression, and distress. Far fewer have examined how emotional states predict test uptake or behavioral responses to test results. Chapter 4 showed that self-referred participants enrolled with greater worry and concern about AD than systematically recruited participants, and that individuals with greater concern were more likely to retain through the earliest steps of the study. Chapter 5 showed that individuals with greater concern about AD and lower coping self-efficacy were more likely to drop out of the study after “prior” does not make sense when it is next to “after” education but before results disclosure. Finally, Chapter 6 found that people who experienced stronger negative reactions to the disclosure of test results were more likely

to make or plan changes to advance planning and health behaviors, and that people who expected testing to provide reassurance reported higher levels of distress and uncertainty after testing than people who expected otherwise.

The importance of emotions in each of the studies in this dissertation may be related to the intimate and personal nature of genetic information compared to other risk factors for disease. How people understand genetics is intimately related to the way they think about kinship and development (Emslie, Hunt, & Watt, 2003; Richards, 1996a, 1996b). Consequently, genetic testing has the power to not only affect how individuals think about disease, but also may change representations of self and families (Shiloh, 2006). In short, genetic information is deeply personal in a way that other types of risk information isn't, and emotional factors may play a much stronger role in determining uptake and behavioral responses. Conceptual models that consider test uptake and behavioral responses from stress and coping perspective have been proposed, but have largely not been used in susceptibility testing research (Baum et al., 1997; Gooding, Organista, Burack, & Biesecker, 2006; Shiloh, 2006). Findings from this dissertation highlight a need to understand the role of emotions in genetic susceptibility testing as more than just important reactions, but also as key determinants of behavioral and other psychosocial outcomes.

An important caveat to this statement is the overlapping and potentially more powerful meaning of AD. AD is different from other common diseases in the way it slowly robs patients of their identities and abilities. The resulting erosion of relationships and the burdens of caregiving can leave close others feeling exhausted, burnt out, and depressed (Ott, Sanders, & Kelber, 2007; Schulz & Williamson, 1991; Takai et al., 2009).

All participants in the second REVEAL Study trial and $\frac{3}{4}$ of participants in the third had a first-degree relative with AD, and the majority of those without an affected FDR still had a family history for the disease. It is likely that susceptibility testing had personal meaning for participants in a way that might not occur with susceptibility testing for other chronic diseases.

THEORETICAL IMPLICATIONS

I based the underlying conceptual model that served as the basis for aims, hypotheses and analyses primarily upon three theories. First, I used Self Determination Theory (SDT) to hypothesize why the process of self-referral may engender greater intrinsic motivation for testing. Second, I used the Elaboration Likelihood Model (ELM) to hypothesize why self-referred individuals – presumably more motivated to receive information provided during pretest education and genetic risk disclosure – would be more affected by it. Finally, I used the Common Sense Model of Self Regulation (CSM) to explain how cognitive and affective differences at enrollment, as well as differential effects of pretest education and genetic risk disclosure by referral process on those factors, would result in greater test uptake and ultimately greater rates of behavior change among self-referred participants. The findings from this dissertation suggest that other theories may be more appropriate for comparing self-referred and systematically recruited populations in genetic susceptibility testing research.

Evidence that the process of self-referral fostered motivation, as would be suggested by SDT, was poor. Data at enrollment showed important demographic differences between self-referred and systematically recruited participants, as well as greater AD worry among self-referred participants. The data suggested no differences on

cognitions about AD, testing, or health behaviors, however. Admittedly, the REVEAL Study did not administer direct measures of motivation, intrinsic or otherwise. Furthermore, the use of different sample frames to enroll the self-referred and systematically recruited cohorts limits my ability to distinguish any psychosocial disparities between the cohorts resulting from the experience of self-referral – as would be suggested by SDT – rather than resulting from enrolling a different population. The lack of differences between cohorts on all cognitions suggests that whatever motivational impact that stems from the experience of self-referral is minor, at best. What differences that were observed in this dissertation are likely the result of enrolling different participants rather than setting a precedent where self-referred participants feel more proactive.

Evidence supporting the use of the ELM to explain the differential impact of pretest education and genetic risk disclosure was also lacking. The analyses in Chapter 6 showed self-referred participants as less likely than systematically recruited participants to discuss prevention during genetic risk disclosure, but more likely to report or plan changes to advance planning and health behaviors. These trends existed only among $\epsilon 4$ carriers, however. Among $\epsilon 4$ -negative participants, the cohorts did not differ in the likelihood of discussing, making, or planning changes to advance planning or health behaviors. ELM would suggest that the impact of information is contingent upon motivation, which presumably is greater among self-referred participants regardless of $\epsilon 4$ carrier status. Furthermore, ELM suggests that emotional arousal can negatively affect the ability of an individual to centrally process messages, but my analyses showed that stronger emotional responses were actually associated with greater rates of advance

planning and health behavior change. ELM was primarily developed to help researchers and interventionists understand the impact of media campaigns where individuals were encountering unsolicited information. Active information seeking is a more appropriate description for what occurs in the REVEAL Study. Assuming so, analyzing responses from a motivated reasoning perspective, as suggested earlier in this chapter, may be more appropriate for explaining the trends observed in these analyses.

Analyses were more favorable regarding the use of CSM to predict changes to advance planning and health behaviors as a function of cognitive and emotional factors, although its utility for describing test uptake is questionable. Chapter 6 showed that pretest expectations, post-test susceptibility and control, and negative post-test affect correlated well with behavioral outcomes of interest, although pretest cognitions were poor predictors of both uptake and health behavior changes. Because analyses were primarily focused on differences between self-referred and systematically recruited participants, I analyzed the correlation between only a few psychosocial factors and behavioral outcomes of interest. Testing of other factors suggested in the underlying conceptual model will need to be a focus of future work, but initial findings presented in this dissertation are promising.

DIRECTIONS FOR FUTURE RESEARCH

This dissertation used data from the REVEAL Study to provide important insight about how enrollment of self-referred populations into genetic susceptibility testing research affects uptake of and response to testing. Addressing limitations that challenge the internal and external validity of results is an important next step to this line of research. The REVEAL Study's admixture of participants drawn from many different

settings (e.g., clinical waiting rooms, research registries, the community at-large) calls into question how much findings reflect differences in sampling frames rather than differences in referral processes. The ideal study of the impact of self-referral would draw from the same universe for both the self-referred and systematically recruited cohorts.

Replicating findings within the current generation of genetic susceptibility tests will also be important. *APOE* genotyping to determine AD risk provides valuable insight about how individuals respond to genetic risk information about common, complex diseases, but the field of genetic susceptibility testing has evolved greatly in recent years. Whereas the REVEAL Study examined a single gene to provide risk information about a single disease, the tests commonly available to the public examine thousands of genetic markers simultaneously to provide information about dozens to hundreds of conditions. Moreover, AD may be poorly representative of other chronic diseases given its lack of proven prevention and treatment strategies. In some ways, the exceptional nature of AD makes this dissertation timely given the recent incorporation of *APOE* genotyping for AD risk into some DTC testing panels, but how individuals respond to *APOE* and AD risk information in isolation is likely to be stronger than the way they would respond to such information while simultaneously receiving risk information about other diseases.

Refining the conceptual model that underpins this dissertation represents an important direction for future research. The model assumed that differences in cognitions about disease, testing and behavior by referral cohort existed at baseline, and that these differences would eventually lead to differences in test uptake and behavioral responses. Differences at enrollment were generally not observed, however. More importantly, baseline cognitions were surprisingly poor predictors of outcomes of interest. Cognitions

at follow-up *were* correlated with outcomes, suggesting that the factors I examined in this dissertation are indeed important determinants, but have more sophisticated relationships than originally proposed. Developing more accurate conceptual models of test uptake and behavioral responses to genetic susceptibility testing will be essential to maximize the potential of genetic susceptibility testing to improve health outcomes.

Another line of future research relates to findings that were counterintuitive. Self-referred $\epsilon 4$ carriers were more likely to report or plan changes to health behaviors than systematically recruited $\epsilon 4$ carriers despite being less likely to discuss prevention during disclosure sessions. Self-referred participants were clearly primed to make health behavior changes in a way that systematically recruited participants were not, but this dissertation provided minimal insight about why. The differences may be attributable to differences in uncertainty observed after testing, but they may also reflect greater (and unmeasured) intrinsic motivation for behavior change, greater self-efficacy about behavior change, or some other mechanism. Semi-structured interviews with participants or qualitative analyses of patient-provider encounters may be fruitful approaches for understanding what makes disclosure of genetic test results to self-referred participants different than disclosure to systematically recruited participants. A better understanding of these differences may help providers communicate test results in ways that are more likely to result in positive health behavior changes.

Finally, the findings about emotions merit greater attention. Participants with greater AD concern were more likely to retain through the initial steps of the study and more likely to drop out after education. $\epsilon 4$ carriers were more likely than non-carriers to make or plan changes to advance planning and health behaviors, but possibly only among

self-referred participants. The emotional differences between referral cohorts identified in this dissertation may be a reflection rather than a determinant of how participants were engaging in the messages communicated during education and disclosure, and may help to explain why self-referred participants responded differently to pretest education and disclosure differently than systematically recruited participants.

CONCLUSION

The utility of genetic susceptibility testing is largely a function of who uses it and how often it leads to informed decision making and improved health behaviors. On the one hand, this dissertation adds to the pessimism that genetic susceptibility testing will evolve into an effective tool for motivating individuals to adopt healthier behaviors at a population level. Studies of genetic susceptibility testing for common, complex disease have largely examined populations that have self-referred to testing, yet have still provided minimal evidence that testing improves health behaviors (Bloss, Madlensky, Schork, & Topol, 2011; McBride, Koehly, Sanderson, & Kaphingst, 2010; Smerecnik, Grispen, & Quaak, 2012). The results from this dissertation suggest that wider promotion of testing to people who demonstrate no prior interest in testing will result in less frequent uptake of testing and lower rates of behavior change than existing research has shown, even among those who are found to be at increased genetic risk.

On the other hand, the results suggest that testing can inform changes to advance planning and health behaviors, at least in certain situations. Many still believe that genetic testing for common, chronic disease could save lives and reduce healthcare costs if it was offered to the right people in the thoughtful ways. The implications of this research are encouraging given recent changes in the field. Although they still

recommend against it, the American College of Medical Genetics and the National Society of Genetic Counselors have softened their stances against *APOE* testing for AD risk, stating, “If a patient wishes to pursue testing despite genetic counseling and recommendations to the contrary, testing may be considered at the clinician’s discretion” (Goldman et al., 2011, p. 601). Moreover, DTC providers have recently added *APOE* testing for AD risk to their panels of tests. Protocols in the REVEAL Study included steps to better ensure the safety of participants that are not always incorporated into clinical practice or consumer services, including mandatory pretest education and screening for mood disorders and the use of a trained clinician (usually a genetic counselor) to communicate test results. Findings from this dissertation nevertheless raise hopes that testing will provide real utility to those who seek it, particularly because the REVEAL Study deliberately omitted any attempt to facilitate behavior change.

This dissertation is also timely in its focus on different ways of making genetic susceptibility information available. Sequencing in clinical practice is approaching (Ashley et al., 2010; Ross, Hambuch, O'Daniel, Murray, & Bentley, 2011), and policymakers are already struggling with questions about what rights individuals have to the information it produces and how to communicate it, particularly for conditions like AD with limited prevention options. Options that have been discussed include proactively soliciting patients’ preferences, akin to systematic recruitment; and reactively withholding information until it is requested, akin to self-referral (Berg, Khoury, & Evans, 2011; Institute of Medicine, 2012). The findings from this dissertation provide a glimpse of the implications of each of these strategies with respect to who shows an interest in the information, who ultimately receives it, and how they respond to it.

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APPENDICES

Appendix 1. Sample recruitment materials.

Recruitment brochure (from the University of Michigan site, 3rd trial)

The REVEAL Study

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study is a federally funded multi-center research project. It examines the impact of using genetic information to help inform individuals about their chances of developing Alzheimer's disease.

The REVEAL Study has been reviewed and approved by the Institutional Review Board of the University of Michigan (U-M) Medical School and the U-M Alzheimer's Disease Research Center.

FOR MORE INFORMATION, CONTACT

Kurt Christensen, MPH
Project Coordinator
University of Michigan
300 North Ingalls SD-04
Ann Arbor, MI 48109-0471
Tel: (734) 763-7726
Fax: (734) 647-7343
Email: hbggenetics@umich.edu

OR visit our website:
stemmaker.umich.edu/hbggenetics/reveal

Risk Evaluation and Assessment for Alzheimer's Disease

REVEAL

Learn About Your Genetic Risk for Alzheimer's Disease

MICHIGAN

WHAT IS THE REVEAL STUDY?

REVEAL (Risk Evaluation and Education for Alzheimer's Disease) is a multi-center NIH-funded research project. The goal of the REVEAL Study is to provide interested adults with genetic susceptibility testing and information about their chances of developing Alzheimer's disease (AD).

Eligible participants will have a phone interview about their attitudes toward Alzheimer's Disease and genetic testing. Participants will be given the opportunity to meet with a genetic counselor to discuss any family history of AD and learn about a gene associated with the condition. Participants will then have the opportunity to have their blood drawn for genetic testing and receive an AD risk assessment.

Information from the REVEAL Study will be used to determine the best ways to educate people about their potential genetic risk for AD.



WHO IS ELIGIBLE TO PARTICIPATE?

Adults between the ages of 18 and 84 who are interested in receiving a genetic risk assessment for Alzheimer's disease may be eligible to participate.



WHAT'S IN IT FOR PARTICIPANTS?

Your participation will provide important information about the impact of providing genetic risk assessments for Alzheimer's disease. Only through participation in research will progress be made in the fight against this devastating condition.

Benefits to participants also include:

- Learning about factors that increase risk for developing Alzheimer's disease.
- Free education about the genetics of AD.
- Free genetic counseling and risk assessment.

PARTICIPATING RESEARCH CENTERS

University of Michigan
(Ann Arbor, MI)

Boston University
(Boston, MA)

Case Western Reserve University
(Cleveland, OH)

Howard University
(Washington, DC)

UNIVERSITY OF MICHIGAN INVESTIGATORS AND STAFF

Scott Roberts, Ph.D.

Principal Investigator

Erin Linnenbringer, M.S., C.G.C.

Genetic Counselor

Kurt Christensen, M.P.H.

Project Coordinator

Sample recruitment mailing letter and reply card (sent to members of the research registry from the Michigan Alzheimer's Disease Research Center)

<date>

Dear <name>:

We are writing you on behalf of our colleagues at the Michigan Alzheimer's Disease Research Center (MADRC). Our research team, which is independent of the MADRC and is based in the University of Michigan School of Public Health, is currently recruiting participants for a clinical trial called the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study. The REVEAL Study is a multi-center NIH-funded research project providing healthy adult children and siblings of Alzheimer's disease (AD) patients with the unique opportunity to receive information about their own chances of developing AD.

Participants of this study will be given the opportunity to learn about genes and other risk factors associated with AD. Participants will then be offered a genetic-based AD risk assessment describing their chance of developing AD in the future.

If you have a parent, brother, or sister who has been affected by AD, you may be eligible for the REVEAL Study.

Enclosed you will find a REVEAL Study brochure which contains more information about the project. If you are interested in hearing more about the study, or if you would like to participate, please call Kurt Christensen or Erin Linnenbringer at (734) 763-7726. You may also e-mail Kurt at kdchrist@umich.edu or Erin at elinnen@umich.edu for more information.

We hope you consider joining us in this research effort to understand how providing AD risk information will affect families affected by this disease. Thank you for your continued interest in AD research here at the University of Michigan.

Sincerely,

Erin Linnenbringer, MS
Certified Genetic Counselor

Kurt Christensen, MPH
Research Assistant

J. Scott Roberts, Ph.D.
Principal Investigator

Name: _____ Date: _____

I received the mailing about the REVEAL - Risk Evaluation and Education for Alzheimer's Disease - Study. I would like to tell you that:

YES! I am interested in participating. Please contact me with more information at the following phone number

I do not want to participate in the REVEAL Study. I am not interested in participating because (optional):

Sample newspaper ad copy (Washington, DC area, 3rd Trial)

Free Alzheimer's disease education and risk assessment provided through a Howard University research study called REVEAL. To be eligible you must have a living or deceased parent or sibling with Alzheimer's disease. Individuals who are interested may call 202-865-0008.

Sample Website Advertisement (University of Michigan “Engage” site for clinical trials)



University of Michigan Clinical Research

Title: REVEAL - Risk Evaluation and Education for Alzheimer's Disease Study

Condition Category: Alzheimer's Disease

Study Description: Recent advances in research on Alzheimer's disease (AD) have brought about the possibility of genetic susceptibility testing for asymptomatic individuals. While such risk assessment is not currently recommended for use in clinical practice, it may become a useful procedure in the future given advances in AD knowledge. The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study is a multi-center research project funded by the National Institutes of Health (NIH) that examines the impact of using genetic information to help inform interested individuals about their chances of developing AD. Study findings will be used to inform practice and policy related to genetic testing for AD and other conditions. We are looking for healthy adults interested in learning about their chances of developing AD. We are primarily interested in first-degree relatives (i.e., siblings or adult children) of living or deceased patients with AD, but other interested parties are encouraged to contact us. Participation in the REVEAL Study occurs across multiple steps, including: • An initial phone interview to determine study eligibility • Education about risk factors for AD • Genetic testing and subsequent risk disclosure from a certified genetic counselor • Follow-up surveys up to one year following risk disclosure Education and counseling are provided free of charge. Participants are reimbursed for parking. No physical exams or medical treatments are required for this study. All study appointments will be held at the U-M Medical Center in Ann Arbor.

Eligibility:

Age Range: From 18 To 84 years

Gender: Male and Female

Ethnicity: All

Race: All

Smoking: Both Smoking and Non Smoking Volunteers

Medication: No Restriction

This study is seeking: healthy subjects

Other Eligibility Factors

Affected family members should have an average age of Alzheimer's disease onset of higher than 60

Must not have a personal history of cognitive impairment, dementia or Alzheimer's disease

Must self-identify as either White/Caucasian and Black/African American

Location of Study Visits: Ann Arbor, MI

Principal Investigator: Roberts, Jeffrey Scott

May 3, 2007 11:31 AM

Sample Newspaper Write Up (Ann Arbor News, June 19, 2007)

VOLUNTEERS - Study on Alzheimer's seeks curious relatives

Ann Arbor News (MI) - Tuesday, June 19, 2007

Researchers in the University of Michigan's School of Public Health are looking for 70 people to participate in a test about Alzheimer's disease.

The subjects will be tested for a genetic variation that predisposes them to Alzheimer's. Researchers are primarily interested in participants who have a parent or sibling who has been diagnosed with it and who are interested in learning more about their own risk, but who are not currently experiencing dementia.

The study includes a series of visits, interviews, a meeting with a genetic counselor and a blood draw for the genotyping. Subjects are followed for one year to determine the psychological and behavioral impact of having the information. Subjects will not be paid, but the test, counseling and follow-ups are all free

The multi-center research initiative is funded through the National Human Genome Research Institute and the National Institute on Aging.

For more information, contact the research team at 734-763-7726; e-mail the team at hbhegenetics@umich.edu, or visit www.sitemaker.umich.edu/hbhegenetics/reveal.

Tracy Davis, News staff reporter

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Record Number: 0416893172

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Appendix 2. Educational brochures used in the second and third REVEAL Study trials.



Understanding Your Risk of Alzheimer's Disease

Alzheimer's disease is a progressive brain disorder that ultimately impairs a person's ability to carry out daily activities; it is the most common cause of memory and language problems (sometimes referred to as "senility" or "dementia") among older people. Although much is known about the disease's biology, and treatments are available for some of its symptoms, there is currently no cure or prevention for Alzheimer's disease. An estimated four million Americans have Alzheimer's disease—a number that is projected to grow to over 13 million by 2050.

Alzheimer's Risk Factors

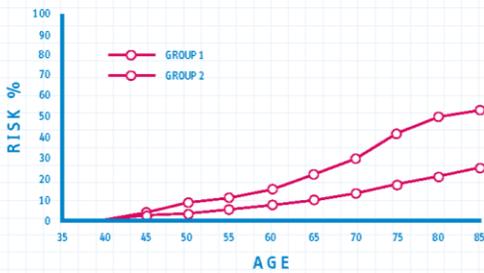
The general population's risk of developing Alzheimer's disease is about 10–15%. This means that for every group of 100 people, on average, 10–15 of them will develop Alzheimer's disease at some point in their life. Some people have a higher or lower risk than the general population. One or more of the following factors can elevate a person's Alzheimer's disease risk above that of the general population:

- Getting older
- Being a woman
- Being African American
- Having a parent, brother, or sister with Alzheimer's disease
- Inheriting a specific form of the APOE gene

However, it is important to remember that if you have one—or even all—of these characteristics, you still may never get Alzheimer's disease.

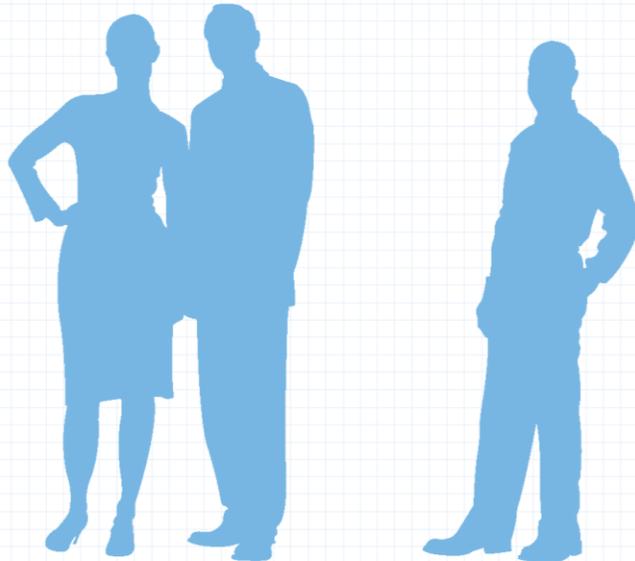
Understanding Your Risk Assessment

You will be given an estimate of your risk of developing Alzheimer's disease by the time you are 85 years old. Depending on your risk factors, you will be given a risk number between approximately 15% to 75%. Your risk estimate will also be shown on a graph, similar to that pictured below.



The characteristics taken into account in the risk assessment include your age, gender, race, APOE test result, and whether or not you have a parent, brother, or sister with Alzheimer's disease.

We are still learning about many other genetic and non-genetic factors that are involved in the development of Alzheimer's disease. As scientists learn more about what causes Alzheimer's disease, this new information may alter your risk assessment.



E2 E4

E3 E4

E4 E4

There are six possible combinations of the three APOE forms. These combinations are called **genotypes**.

Alzheimer's Disease and the APOE Gene

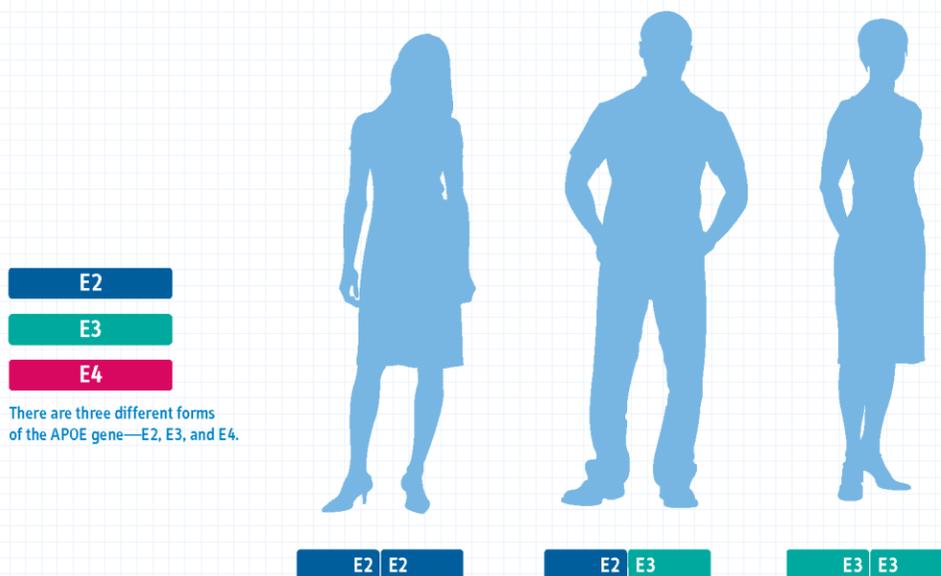
Inheriting a specific form of the APOE gene can increase the risk of getting Alzheimer's disease. The role of the APOE gene in Alzheimer's disease is still being studied. Some studies have shown that it may be related to other conditions in addition to Alzheimer's disease.

We do know that the APOE gene comes in three different forms: E2, E3, and E4. Every person has two copies of the APOE gene—one inherited from each parent. Because there are three different forms of the APOE gene and there are two APOE genes in every person, an individual possesses one of six unique APOE combinations (pictured below).

If an individual has one or two copies of the E4 form of the APOE gene, it increases his or her risk of developing Alzheimer's disease. However, this does not mean that he or she will definitely get Alzheimer's disease.

APOE Genetic Testing

As part of your risk assessment, we provide APOE testing. There are three basic steps to APOE testing. First, you will meet with a genetic counselor to review any questions or concerns about having an Alzheimer's disease risk assessment, including APOE testing. Next, you will provide a small blood sample for APOE testing. Finally, you will meet with a clinician to learn and discuss your test result and risk assessment. Test results are typically available within a few weeks of the blood draw.



Issues to Consider

You may want to consider several issues before having a risk assessment for Alzheimer's disease. Your risk profile is only an interpretation based on our current knowledge and will not give you a simple "yes" or "no" answer, nor will it indicate at what age Alzheimer's disease may develop. There are no proven ways to prevent Alzheimer's disease from developing.

Risk assessment with APOE testing has some limitations:

- You may find it harder to cope with your concerns about developing Alzheimer's disease after having your risk assessment
- Because the risk assessment is based on complex information, it is possible that you or your loved one may misinterpret the results, causing undue stress or false reassurance about your chances of developing Alzheimer's disease
- Confidentiality laws protect APOE test results generated for research purposes. However, if you tell others about your results, there is no guarantee that your results will remain confidential
- Employers or insurance companies could ask you about your risk information and use it to deny insurance coverage or change your policy rates, although it is not a common practice.

There may also be some benefits to receiving your risk estimate:

- It may encourage you to stay abreast of new developments in Alzheimer's disease treatment and prevention, and may motivate you to engage in activities that might help prevent or delay the onset of Alzheimer's disease
- It may satisfy your curiosity about your chances of developing the disease
- You may use your risk assessment to help make long term decisions
- Receiving a lower risk estimate may reduce your anxiety about developing the disease.



Resources

Contact the following organizations to learn more about Alzheimer's disease.

Alzheimer's Association
800-272-3900
alz.org

Alzheimer's Disease Education & Referral Center (ADEAR), a service of the National Institute on Aging (NIA).
800-438-4380
alzheimers.org



The general population's lifetime risk of developing Alzheimer's disease is about 12%.

Understanding Your Risk of Alzheimer's Disease

Alzheimer's disease is a brain disease that is the most common cause of memory and language problems in older people. It can impair a person's ability to carry out daily activities. Although we are learning more about the cause of the disease, and treatments are available for some of its symptoms, there is currently no cure or prevention for Alzheimer's disease. An estimated 5 million Americans have Alzheimer's disease - a number that is projected to grow to over 13 million by 2050.

Who is at Risk for Alzheimer's Disease?

The risk of developing Alzheimer's disease in the general population is about 12%. This means that for every group of 100 people, 12 of them will develop Alzheimer's disease at some point in their life.

Studies have shown that certain groups of people have higher than average rates of Alzheimer's disease, although the reasons for this are still to be determined. Research suggests that the following groups are at elevated risk of Alzheimer's disease:

- Older adults
- Women
- African Americans
- People with a parent or sibling affected by Alzheimer's disease
- People with a specific form of the APOE gene
- People with existing memory problems

However, it is important to remember that even if you are a member of one or more of these groups, you may still never develop Alzheimer's disease.

Alzheimer's Disease and the APOE Gene

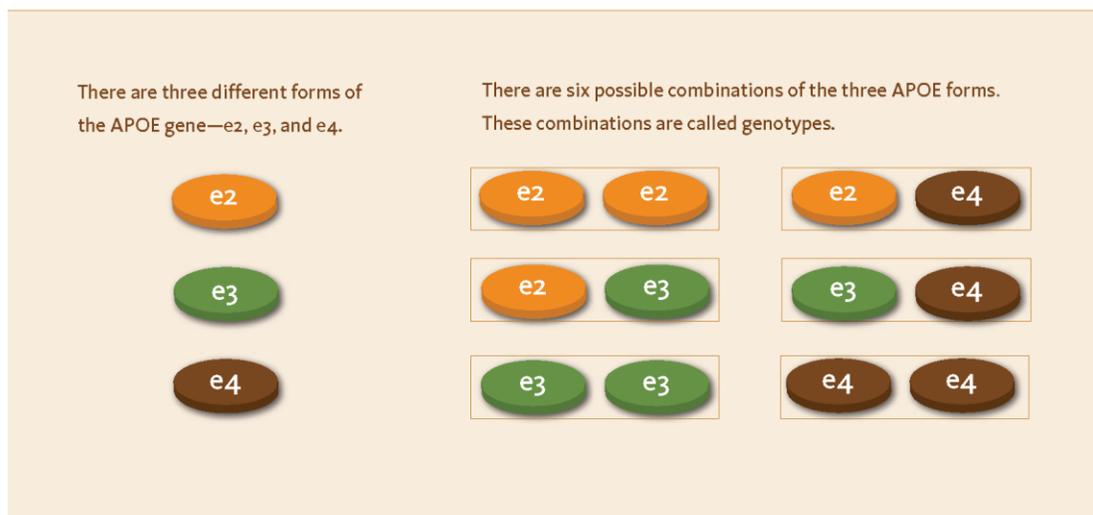
Inheriting a specific form of the APOE gene can increase the risk of getting Alzheimer's disease. The APOE gene's specific role in Alzheimer's disease is still being studied. Some studies have shown that it may be related to other conditions in addition to Alzheimer's disease.

We do know that the APOE gene comes in three different forms: e2, e3, and e4. Every person has two copies of the APOE gene—one inherited from each parent. Thus, an individual can have one of six possible combinations of the APOE gene (pictured below).

An individual who carries one or two copies of the e4 form of the APOE gene is at increased risk of developing Alzheimer's disease.

APOE Genetic Testing

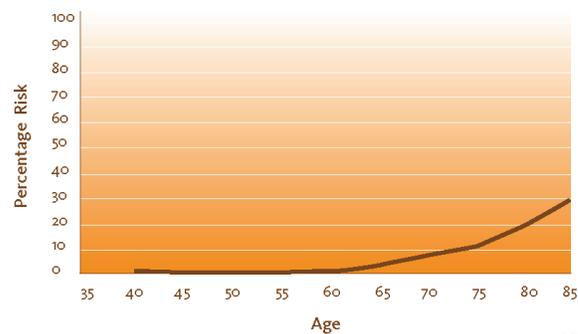
As part of your risk assessment, we provide APOE testing. There are three basic steps to APOE testing. First, you meet with a genetic counselor to review your family history and any questions or concerns that you have. Next, you provide a small blood sample for APOE testing. Test results are typically available within a few weeks of the blood draw. Finally, you meet with a clinician to learn and discuss your test result and risk assessment.



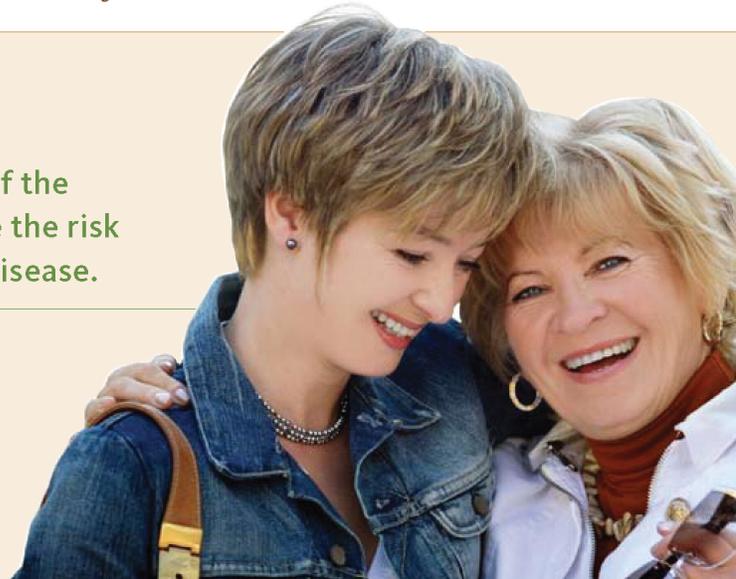
Understanding Your Risk Assessment

You will be given an estimate of your risk of developing Alzheimer's disease by the time you are 85 years old. Depending on your risk factors, you will be given a risk number ranging from 10% to 77%. Your risk will also be shown on a graph, similar to the one pictured below, to help illustrate your risk according to your age.

The characteristics taken into account in the risk assessment include your age, gender, ethnicity, APOE test result, whether or not you have a parent, brother, or sister with Alzheimer's disease, and whether or not you have existing memory problems. We are still learning about many other genetic and non-genetic factors that are involved in the development of Alzheimer's disease. As scientists learn more about what causes Alzheimer's disease, this new information may alter your risk assessment.



Inheriting the e4 form of the APOE gene can increase the risk of getting Alzheimer's disease.



Factors to Consider

You may want to consider several factors before having a risk assessment for Alzheimer's disease. Certain limitations are inherent in the process. Your risk profile is an interpretation based on our current knowledge and will not give you a simple "yes" or "no" answer, nor will it indicate at what age Alzheimer's disease may develop. There are no proven ways to prevent Alzheimer's disease from developing. Other factors to take into account include:

- You may find it harder to cope with your concerns about developing Alzheimer's disease after having your risk assessment
- Because the risk assessment is based on complex information, you or your loved one may misinterpret the results, causing undue stress or false reassurance about your chances of developing Alzheimer's disease
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- Although it is not a common practice, employers or insurance companies could ask you about your risk information and use it to deny insurance coverage or change your policy rates.

There are also some advantages to receiving your risk estimate. Consider that:

- It may encourage you to stay abreast of new developments in Alzheimer's disease treatment and prevention and make long term planning decisions,
- It may satisfy your curiosity about your chances of developing the disease,
- You may be motivated by your risk estimate to engage in activities that might help prevent or delay the onset of Alzheimer's disease, and
- Receiving a lower risk estimate may reduce your anxiety about developing the disease.



Resources

Contact the following organizations to learn more about Alzheimer's disease.

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This brochure was produced as part of the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study based at Boston University Medical Center
<http://www.bu.edu/alzresearch>

This research was funded by the Ethical, Legal and Social Implications branch of the National Human Genome Research Institute (NHGRI)
<http://www.genome.gov>