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Estimating and disclosing the risk of developing Alzheimer's disease: challenges, controversies and future directions

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Abstract

With Alzheimer's disease increasing in prevalence and public awareness, more people are becoming interested in learning their chances of developing this condition. Disclosing Alzheimer's disease risk has been discouraged because of the limited predictive value of available tests, lack of prevention and treatment options, and concerns regarding potential psychological and social harms. However, challenges to this status quo include the availability of direct-to-consumer health risk information (e.g., genetic susceptibility tests), as well as a growing literature suggesting that people seeking risk information for Alzheimer's disease through formal education and counseling protocols generally find it useful and do not experience adverse effects. This paper reviews current and potential methods of risk assessment for Alzheimer's disease, discusses the process and impact of disclosing risk to interested patients and consumers, and considers the practical and ethical challenges in this emerging area. Anticipated future directions are addressed.

Keywords

Alzheimer's disease; genetic testing; risk assessment; risk communication

A major public health concern is the anticipated increase in cases of Alzheimer's disease (AD). Given that the number of older adults will dramatically rise over the next few decades, particularly the 'oldest old' (i.e., 85 years and above), it is critical to prepare for the strain that AD will pose on healthcare systems, caregivers and society at large [1,2]. An important goal within this effort involves risk assessment for asymptomatic adults and patients with preclinical AD. For the purposes of this paper, we define risk as the likelihood of developing clinical (not neuropathological) AD, and risk factors as those that are associated with higher likelihood of later disease, even if their role in the pathophysiology of AD is unclear. Although we recognize the utility in other contexts of demarcating age-dependent versus age-independent risk factors, we do not make this distinction here; in addition, we do not address factors associated with more rapid progress through the various stages of the disease course once it has been identified. Identifying risk factors and at-risk populations has numerous potential benefits. For example, utilizing at-risk populations in clinical trials could enhance the efficiency of prevention efforts by reducing study sample sizes and length of follow-up. Health promotion efforts encouraging

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positive behavior changes could be tailored to individuals possessing putative modifiable risk factors for AD. Learning about one's AD risk might also be useful to certain individuals engaged in financial, insurance and healthcare planning for later life. Surveys of individuals at risk for AD have found significant interest in predictive testing even in the absence of proven means of preventing or delaying disease onset [3]. Test precision and accuracy are key factors here, suggesting that individuals are not just interested in whether or not they will develop AD, but also when.

Currently, few people receive risk assessment for AD because it is not performed as part of standard healthcare. One reason is because known risk factors are not sufficiently sensitive or specific to reliably identify high-risk individuals. More important, there are currently no proven means of preventing or modifying AD risk, so risk assessment does not inform medical care options (i.e., it lacks clinical utility). However, this status quo is likely to change in forthcoming years for several reasons. First, our understanding of the etiology and risk factors of AD are rapidly evolving. Research from basic neuroscience to social epidemiology has shed light on numerous potential causes of AD [4]. Second, treatment options are being vigorously pursued through an increasing variety of clinical trials. Agents to modify disease, delay its onset, and possibly even prevent AD are in development at several major pharmaceutical companies. Third, companies now offer methods of disease risk assessment that bypass the healthcare system and are marketed direct-to-consumer (DTC) [5]. Such methods typically involve DNA testing and analysis of single nucleotide polymorphisms (SNPs) to generate relative risk estimates for common, complex diseases including AD. While the DTC genetic testing industry has attracted much controversy, it is part of a growing movement to increase access to personal health information via emerging information technologies. Given these three trends, it seems likely that disclosure of personal AD risk will occur on a more frequent basis in upcoming years.

The goal of this paper is to examine scientific, practical and ethical issues involved in disclosing risk for AD. In the first section, established and candidate risk and protective factors are reviewed, encompassing varied levels of analysis. The second section will discuss current and potential future methods of risk assessment. The third section will address the small but growing literature on the psychological and behavioral impact of providing risk information for AD. A concluding section will summarize findings in the field and speculate on likely future directions. Throughout the paper, the challenges and controversies involved in generating and disclosing risk will be highlighted.

Risk & protective factors for AD

A comprehensive review of risk factors for AD is beyond the scope of this paper. However, a brief review of selected established and candidate risk factors will facilitate later discussion of the methods of estimating risk for AD. Potential risk and protective factors not addressed in this review include (but are not limited to) personal history of head trauma with loss of consciousness, depression, hypothyroidism, severe headache and estrogen-replacement therapy (see outside reviews for more information) [2,4,6,7]. Risk and protective factors are categorized into the following interrelated domains (TABLE 1):

- Demographic factors
- Cognitive reserve
- Genetics and family history
- Vascular and inflammatory factors
- Diet and physical activity

- Social characteristics

Demographic factors

Although we recognize that variables such as aging and race/ethnicity are proxies for genetic and environmental agents that influence probability of disease, we will begin with a consideration of these demographic risk factors. Aging is the most prominent risk factor for AD, with the vast majority of incident cases occurring in later life. Prevalence of AD is thought to double every 5 years beyond the age of 65 years [6]. Females have a higher prevalence of AD than men [7], with debate regarding whether this difference is largely attributable to longer life expectancy among females. Studies reporting relative risks for race/ethnicity suggest that in the absence of an apolipoprotein E (*APOE*) $\epsilon 4$ allele, older African-Americans have 4.4-times and older Hispanics have 2.3-times the education- and sex-adjusted cumulative risk of older whites, while cumulative risks are similar across race/ethnicity in the presence of an *APOE* $\epsilon 4$ allele [8,9]. However, interpretation of such findings is complicated by selection biases, small racial/ethnic sample sizes, differences in environmental exposures, and confounding by educational attainment and socioeconomic status (SES), which are associated with AD risk [10,11]. For example, Yoruba in Africa have incidence rates less than half of those found among African-Americans, which may be attributable to the stronger influence of *APOE* $\epsilon 4$ and higher cardiovascular risk among African-Americans compared with Yoruba [12].

The association of higher levels of education with lower rates of AD has spawned the ‘cognitive reserve’ hypothesis [13]. According to this theory, cognitive reserve serves as a mediator between brain pathology and clinically expressed AD. Individual cognitive differences may be reflected in the efficiency, capacity, or flexibility of neural networks, or in neural compensation whereby affected individuals use alternate brain structures or neural networks to process information when pathology prevents the use of usual pathways. Cognitive reserve is a likely mechanism by which healthy behaviors, such as physical activity, intellectual activity and socializing, maintain cognitive ability or slow the rate of cognitive decline [13]. Proxy measures of cognitive reserve are lifetime experience, literacy and education level attained.

Genetics & family history

Genetic epidemiology research in the 1990s validated family history as a prominent risk factor for AD; more specifically, presence of an affected first-degree relative (i.e., biological parent or sibling) is associated with a lifetime AD risk of 30–40%, compared with 10–15% in the general population [14]. Some rare early-onset forms of AD (before 65 years of age, and in most cases before 50 years of age) have primary genetic causes, with an autosomal dominant pattern. Such cases of familial AD are very rare in the general population, however, accounting for approximately 2% of all AD cases [15]. The rare mutations that almost inevitably lead to AD in carriers have been discovered in three genes: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes [16].

Research has also identified over 550 possible susceptibility genes for AD [17]. The majority of these genes associated with late-onset AD influence risk only slightly, and not all findings have been replicated [18]. The most established genetic risk factor for the more common, late-onset AD is the *APOE* locus, which has three alleles ($\epsilon 2$, $\epsilon 3$ or $\epsilon 4$) that influence AD risk [19,20]. The *APOE* $\epsilon 4$ allele has been shown in hundreds of studies to have a gene-dose effect on AD risk, whereas the $\epsilon 2$ allele appears to have a modest protective risk. Estimates of genotype-specific relative risks suggest that compared with the most common genotype ($\epsilon 3/\epsilon 3$), the $\epsilon 4/\epsilon 4$ type is associated with an 8- to 15-fold increased risk, while the $\epsilon 3/\epsilon 4$ type confers an approximate two- to threefold increase in risk [18,20,21]. Genotype-specific risks have also been shown to vary by sex and age, with lower age of disease onset associated with the $\epsilon 4$

allele in a dose-dependent manner (i.e., homozygotes have a lower mean age of onset than heterozygotes). The influence of $\epsilon 4$ on AD risk diminishes past 70 years of age, prompting some researchers to conclude that *APOE* affects when, not whether, someone will develop the disease [22]. Although the presence of the $\epsilon 4$ allele(s) significantly increases AD risk, it is neither necessary nor sufficient to cause the disease [20]. More recent research has investigated genetic markers (e.g., rs429358) [17,23–25] as well as other susceptibility genes (e.g., *CLU*, *PICALM*, *SORL1*, *TOMM40*) [18]. Many of these have been identified via genome-wide association studies and await replication in subsequent studies, and their impact on AD risk is considerably smaller than *APOE* (i.e., their effect sizes are represented by odds ratios of less than 1.5).

Vascular & inflammatory factors

Observational studies have shown that vascular risk factors and diseases such as stroke, Type 2 diabetes, hypertension and obesity may also contribute to risk of AD [26]. It has also been suggested that many AD diagnoses may actually represent ‘mixed’ dementias including both AD and vascular pathology [27,28], prompting the investigation of medications traditionally used for heart disease and diabetes (e.g., statins). Additionally, animal and observational studies have suggested a link between inflammatory processes and cognitive decline [29]; a large case–control study found an association between use of nonsteroidal anti-inflammatory drugs (NSAIDs) and lower incidence of AD with a 0.2 (0.05–0.83) risk reduction [30]. However, this protective association may be due to confounders or a select few NSAIDs because clinical trials using NSAIDs have been unsuccessful [31,32]. Randomized controlled trials of antihypertensives, statins, antioxidants and NSAIDs have found these agents to be ineffective in improving cognition and reducing AD risk [26]. A notable example is the multisite Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT) of men and women aged 70 years and over without cognitive impairment but with family history of AD. This study found that the NSAIDs naproxen sodium and celecoxib did not significantly reduce AD risk or improve cognitive function over time compared with placebo and, in fact, had trends toward poorer cognitive scores [31].

Lifestyle factors: diet, physical activity & social characteristics

Social epidemiology studies have suggested that one’s lifestyle may influence expression of AD. A systematic review of 37 community-based prospective studies of adults aged 65 years and over classified several health behaviors as protective or harmful in the risk for cognitive impairment and AD [33]. Risk reducing behaviors were vegetable and fish consumption, moderate alcohol consumption and leisure time physical activity at a moderate level or higher. Behaviors increasing risk include a high saturated fat diet, no or heavy/frequent alcohol consumption, smoking and midlife obesity. There is also suggestion that some of these behaviors may interact with *APOE* genotype to affect risk [34].

Current evidence suggests protective effects of light-to-moderate consumption of alcohol (one to two drinks per day) for cognitive decline, predementia syndromes, and vascular dementia [35], mostly among adults with neither cognitive impairment nor an *APOE* $\epsilon 4$ allele [33,36]. A meta-analysis of 15 prospective studies comparing light-to-moderate drinkers with nondrinkers reported a pooled relative risk of 0.72 (0.61–0.86) for AD [37]. Some studies have found that diets or dietary supplements rich in vitamins C and E may be protective against AD, but these findings have not always been replicated [38]. Diets associated with lower AD risk, such as the Mediterranean diet or Dietary Approaches to Stop Hypertension (DASH) diet, are rich in fruits, vegetables, whole grains, antioxidants, omega-3 polyunsaturated fatty acids and anti-inflammatory compounds (e.g., curcumin) and are low in fat and added sugar [26].

With regard to physical activity, a population-based, prospective cohort study of cognitively normal, elderly adults showed that those who exercised for at least 15 minutes three or more times per week had a lower incidence of AD (13.0 per 1000 person-years) than those who exercised fewer than three-times per week (19.7 per 1000 person-years) [39]. The risk reduction from healthy diet and physical activity could be due to angiogenesis, creation of neural synapses, lower rates of chronic disease and association with other healthy behaviors.

A review of longitudinal observational studies on social network, nonphysical leisure activities, and physical activities – as well as two recent exercise studies – concluded that social, mental and physical activity can be protective against AD and improve cognition [40–42]. These three activities may also improve vascular health and protect against stress, which reduces the risk for AD. Social activity may benefit cognitive health via intermediate pathways that involve behaviors, psychology and physiology, such as cognitive reserve. A study of older adults without dementia found that while level of perceived social support and social network size were not independently associated with cognitive functioning, frequent social engagement was associated with better outcomes in multiple cognitive domains [43]. Finally, a large, longitudinal multicenter study concluded that engagement in cognitively stimulating leisure activities was associated with reduced risk of developing dementia over a 4-year follow-up [44].

Although the preceding review suggests numerous potential interventions to reduce risk, none have been proven effective to date in prospective clinical trials. This may be because studies on lifestyle and health behaviors are often limited by use of self-reported rather than objective measures of predictor variables, number of cognitive assessments, samples that were clinic-based or not representative of the general population, and lack of control for potential confounders [33]. For example, only 37 of 115 studies reviewed by Lee *et al.* met high-quality criteria for their sample, follow-up, assessments and control variables [33]. Nevertheless, the literature on lifestyle risk factors for AD has prompted several different behavioral approaches to enhance ‘brain health.’ The US national Alzheimer’s Association has promoted a ‘Maintain Your Brain’ campaign to encourage lifestyle modifications including staying physically, socially, and mentally active and adopting a brain-healthy diet [201]. Although lacking demonstrated efficacy in reducing AD risk, they are nonetheless recommended for possible cognitive benefits and also the proven positive impact on other areas of health [45].

Methods of risk assessment for AD

The preceding review suggests several possible methods for identifying populations at risk for AD and providing quantitative risk estimates. These methods will be reviewed across four categories (TABLE 2):

- Epidemiological approaches;
- Predictive genetic testing;
- Other biomarkers;
- Clinical assessment of mild cognitive impairment (MCI).

The first two methods apply anytime during adulthood to generate lifetime risk estimates for AD. The latter two are useful only in the preclinical phase of AD, where observable brain pathology or mild memory impairment is present, and conversion to clinical AD is the outcome of interest. The latter two would presumably involve a much shorter time interval (and older adult recipients) than risk estimates derived from the former two methods.

Epidemiological approaches

The development of a risk algorithm based on factors identified from a large body of epidemiological research has been used in other common diseases. Demographic and behavioral factors are combined to yield a quantitative (e.g., percent lifetime risk) or qualitative (categorization as low, average or high risk) risk estimate. Risk factors can usually be easily ascertained by self-report, thus lowering the cost and expanding the reach of assessment. A well-known example is the 'Your Disease Risk' website [202] developed by researchers at the Harvard School of Public Health, which uses an online questionnaire to generate risk estimates for five common, complex diseases. Users enter their demographic characteristics, health history, and health behaviors to yield both a risk estimate and recommendations for prevention and risk reduction. Such an approach might be relevant in AD given the presence of several established and candidate risk and protective factors (TABLE 1). Generating a richer epidemiological database on which to base such estimates will be a challenge, however. Owing to its focus on clinical rather than population-based studies, AD research samples have typically been biased to include a disproportionately low number of racial/ethnic minorities and persons of lower SES. In addition, environmental exposure and behavioral variables have been inconsistently measured across studies (or not measured at all). The quality of risk assessment from epidemiological approaches will improve if such limitations are addressed.

Predictive genetic testing

Genetic testing for AD risk already occurs in a rare number of families affected by autosomal dominant forms [46]. The genetic counseling paradigm initially developed for Huntington's disease (HD), described later, has been successfully adapted for use with these family members [47]. Yet for most asymptomatic adults seeking genetic risk for AD, susceptibility testing using *APOE* genotyping would be more relevant. Approximately a quarter of the general population carries the risk-conferring $\epsilon 4$ allele, yet such a test result provides much less certain risk information than testing for the less common mutations in *APP*, *PSEN1* or *PSEN2* genes [48]. The limited test predictive value, coupled with a general lack of treatment options for AD, prompted consensus statements in the 1990s from leading experts in the field cautioning against the premature introduction of *APOE* susceptibility testing in asymptomatic individuals [49–51], and these guidelines are still followed today. *APOE* testing is therefore still used primarily for research purposes. In clinical practice, the patented *APOE* test [301] is marketed only to confirm diagnosis in affected AD patients. However, several recent developments promoted renewed interest in *APOE* testing. First, at least three companies have marketed DTC genetic tests for AD, marking the first access to susceptibility testing for late-onset AD outside of medical care or research [52]. Experts in the field have criticized both the analytic and clinical validity of this testing [53]. For example, some platforms do not directly assess *APOE* genotype but rather proximal SNPs found in linkage disequilibrium with *APOE* [53]. Furthermore, risk estimates provided to customers are typically based on GWAS alone and lack formal validation studies to confirm their predictive value. For some, motivations for seeking testing may override these test limitations. Although the US Congress passed the Genetic Information Nondiscrimination Act (GINA) in 2008 to protect against discriminatory use of genetic testing by health insurers and employers, this legislation does not address life, disability or long-term care (LTC) insurance [54]. Thus, people may seek DTC genetic testing services to avoid potential discrimination resulting from genetic information being accessed from their medical records. LTC insurance companies, in particular, might find *APOE* genotyping results of interest, with actuarial justification to support coverage and cost decisions based on test results [55,56]. These developments, as well as the prospect of future treatment advances and increased understanding of genetic contributions to AD, suggest the importance of psychosocial research and policy work regarding genetic risk assessment for AD [57].

Other biomarkers

The role of biomarkers in clinical care for AD is to aid early detection, diagnosis, disease progression and pharmacogenomics [24,58]. A confirmed biomarker should be associated with AD neuropathology by detecting it, presenting itself in confirmed AD cases, and measuring therapeutic effects on pathology. A biomarker test should have a sensitivity, specificity and positive predictive value greater than 80% and be noninvasive, simple, reliable, reproducible and inexpensive to perform [59,60]. Biomarkers for AD include proteome features such as biochemical proteins, peptides and metabolites in biological fluids. Specific examples are the well-known amyloid- β (A β) proteins, responsible for senile neuritic plaques, and tau, responsible for neurofibrillary tangles [61]. Additional biomarker proteins include acute phase proteins, homocysteine, total cholesterol, isoprostanes and cytokines [62]. Neuroimaging detects structural and functional brain features that serve as biomarkers of AD risk or pathology; relevant here are brain structure volumes of the hippocampus, entorhinal cortex, basal forebrain nuclei and cortex [59].

Biomarkers detected in CSF by a lumbar puncture and PET neuroimaging appear to be promising techniques for early detection, classifying asymptomatic adults and patients with preclinical AD for primary prevention [63]. PET imaging detects Pittsburgh Compound-B (PIB), a radioligand to A β in the brain [64,65]. While PIB primarily marks AD pathology in affected patients, neuroimages have detected PIB in several asymptomatic research participants, suggesting a future use of PIB to identify high-risk persons who do not yet show other clinical evidence of AD. However, PIB, like hundreds of other biomarkers, has not yet been validated for clinical purposes and is therefore not disclosed to research participants. Even if such markers are validated, their detection will likely rely on specialty care providers and expensive technologies, thus limiting their reach and impact. With regard to CSF markers, CSF A β_{1-42} (in combination with t-tau and number of *APOE* $\epsilon 4$ alleles) is a predictor of progression to mild AD from normal cognition or MCI [16]. The positive predictive value of CSF A β_{1-42} ranged from 62–82% in two notable studies [60,61]. However, such studies may be limited by the potentially confounding associations of CSF A β levels with age and number of *APOE* $\epsilon 4$ alleles.

Clinical assessment of mild cognitive impairment

Another means of identifying persons in the preclinical stages of AD is through expert clinical assessment of MCI, the often transitional state between normal cognitive aging and AD [66, 67]. Diagnosis of MCI can be challenging; identification of patients is reliably achieved by specialty care clinicians drawing upon a detailed history from an informant, neurological examination, and comprehensive neuropsychological assessment. Although some critics of the MCI concept contend that it is an early form of AD (rather than a risk factor) [3,68], MCI has emerged as a clinical entity. The International Classification of Diseases (ICD)-9 has a MCI billing code (331.83), and surveys of practicing geriatricians and neurologists suggest that it is being regularly utilized [69–72]. Such physicians report that they often discuss AD risk in their clinical encounters with persons with the amnesic form of MCI, who are at high risk of developing AD, with annual conversion rates estimated at approximately 10–15% and a high lifetime risk of 80% or more [59,73]. However, longitudinal follow-up in MCI studies typically does not extend beyond 3 years, and population-based research of this group is rare, thus limiting the quality of risk estimates that can be provided. Two longitudinal studies in progress are the Alzheimer's Disease Neuroimaging Initiative (ADNI) and Mayo Clinic Study of Aging [74,75].

Impact of risk assessment for Huntington's disease

Before discussing the literature on the psychological and behavioral impact of risk assessment for AD, it is worth considering the much more developed literature on another fatal, incurable, adult-onset neuropsychiatric condition where genetic causes are strongly implicated: HD. Clinical protocols for presymptomatic, predictive testing for HD – including extensive and time-consuming highly structured pre- and post-test counseling guidelines – have been extensively researched and routinely offered as a clinical service since the early 1990s. Gene identification now permits highly accurate (near 100%) positive predictive value in risk assessment for at-risk family members of HD patients [76,77]. A review of the HD risk assessment literature suggests the following:

- Although initial test interest is high, uptake rates are relatively low (9–20%), with over-representation of women and more highly educated persons;
- People who pursue testing generally show better psychological functioning than those who decline;
- Carriers experience greater transient distress following risk disclosure, but by 6 months both carriers and noncarriers are generally without negative psychological effects of testing;
- Psychological adjustment at baseline (e.g., level of depression or hopelessness) is a better predictor of post-test adjustment than the test result itself [78].

Such research has shown that predictive testing for HD has had fewer adverse outcomes than initially feared when it was introduced [79].

However, this is not to say that test results are benign or recipients do not sometimes experience significant distress as a result of undergoing risk assessment. A worldwide assessment of adverse psychiatric outcomes showed that approximately 1% of 4527 HD test participants experienced catastrophic events (i.e., attempted or completed suicide, psychiatric hospitalization) following testing; the vast majority of these participants had received a positive test result [80]. Even disclosure of low risk can be stressful, if participants experience 'survivor guilt' or regret over irreversible decisions made with the assumption that they would develop HD [81]. Furthermore, the impact of testing on people without post-test counseling is unknown. A study of psychological outcomes 7–10 years following predictive testing suggests that distress levels are higher than in the 2–3 years immediately following testing, presumably because individuals are closer to the likely age of disease onset [82]. This finding suggests a need for longer-term follow-up than is typically undertaken. The HD paradigm of genetic counseling and genetic testing has been the dominant model in the consideration of risk assessment of AD; however, some important distinctions between the two are raised in the next section.

Impact of risk assessment for AD: the REVEAL Study

Because AD risk assessment is not typically performed in a clinical setting, little research has been conducted on its psychological and behavioral impact. Most research in this area has focused on genetic testing. Following the identification of *APOE* and higher penetrance genetic mutations in the 1990s, interest in genetic risk assessment was assessed by surveys posing hypothetical genetic testing scenarios [83]. A survey of 203 first-degree relatives of people with AD found that a majority of participants expressed intentions to pursue risk assessment across various scenarios, with perceived pros outweighing cons [72]. A general population telephone survey found that 79% of respondents expressed interest in predictive genetic testing for AD and that they would pay on average more than US\$300 for such a test [3]. However, as the HD experience demonstrated, intentions to pursue testing expressed in survey research

often do not translate into actual test uptake [84]. It is therefore important to look at clinical research where risk assessment for AD is actually offered to interested persons.

The Risk Evaluation and Education for Alzheimer's disease (REVEAL) Study, continuously funded by the National Institutes of Health since 1999, is a series of multisite randomized clinical trials designed to assess the impact of *APOE* genotype disclosure and related risk communications. An interdisciplinary team of clinicians, geneticists, genetic counselors (GCs), health psychologists, ethicists and policy scholars created and evaluated empirical data on the impact and use of *APOE* disclosure for evaluating the AD risk. Risk estimates up to age 85 years (range: 13–57%) were derived from a longstanding multisite program of genetic epidemiology research [8,85]. Education and genetic counseling were delivered at each site by formally trained GCs. In a sample of 162 adult children of people with AD, the first REVEAL trial assessed the psychological and behavioral impact risk assessment incorporating *APOE* genotype (genotype disclosure [GD] group) versus risk assessment based on age, gender and family history alone (genotype non-disclosure [GND] group).

Risk assessment motivations & uptake

Prior to risk disclosure, participants were asked to rate the importance of reasons for and against seeking genetic risk assessment for AD. Reasons listed were derived from the group's prior surveys on the topic, which found that they rated test pros much higher than test cons and that nonmedical reasons were key motivations [86]. The most commonly endorsed reasons in this study included:

- To arrange personal affairs (87.4%);
- The hope that effective treatment will be developed (86.8%);
- To arrange LTC (81.4%);
- To prepare family for the possibility of illness (77.8%);
- To do things sooner than planned (75.0%);
- Relief if found to be at lower risk (69.6%).

Limited clinical utility is a main reason for withholding risk assessment for AD. However, of interest here is that participants commonly cited reasons related to personal utility; they believed that information could be helpful in planning for the future even if there were no proven medical care options to reduce their AD risk.

In terms of test uptake, approximately one in four (24%) systematically ascertained participants pursued risk assessment by enrolling in the RCT and receiving risk disclosure [87]. This rate of uptake is well below those observed in studies of genetic testing for diseases where treatment options are available (e.g., hereditary breast and colon cancers), but on the higher end of test uptake estimates for disorders without proven treatment options. Overall, participants were disproportionately female, white, of high socioeconomic status and of lower age (<60 years), suggesting stronger test interest and/or access to clinical research opportunities among these groups. Again, these results are consistent with other studies examining demographic predictors of test uptake [88,89].

Psychological impact

A prominent reason given in consensus statements recommending against clinical genetic testing for AD was concern regarding potential psychological harms of disclosing risk information for a severe and incurable disorder [90]. The primary outcome of the first trial was therefore psychological impact of risk assessment. Validated self-report measures of anxiety, depression symptoms and test-related distress were administered 6 weeks, 6 months and 1 year

after disclosure. Results showed no difference in changes in the time-averaged measures between GD and GND groups. Secondary comparisons between those receiving *APOE* $\epsilon 4+$ results (GD $\epsilon 4+$) and the GND group also showed no significant differences, while the GD $\epsilon 4-$ group showed significantly lower test-related distress when compared with the GD $\epsilon 4+$ group. These results suggest that disclosure of *APOE* genotype under carefully controlled circumstances to adult children of persons with AD did not pose significant psychological risks, even for those who learned they were *APOE* $\epsilon 4+$ [91].

These findings are consistent with the only other published study of psychological impact of *APOE* disclosure, a prospective longitudinal cohort study of 76 asymptomatic individuals that did not find any significant adverse emotional reactions to risk information beyond 1 month [92]. The REVEAL findings are also largely consistent with research on the psychological impact of genetic risk assessment for other adult-onset disorders. While much attention can be focused on the potential impact of 'bad news' from a positive genetic test result, oftentimes baseline psychological functioning is a better predictor of post-test response than test result itself, as was the case in REVEAL. Research across several disorders including HD and hereditary cancer syndromes has suggested that test-related distress, while sometimes significant, is usually transient if patients are provided proper post-test counseling [93,94]. If test results match expectations, then even positive results for severe disorders are usually not overwhelming. However, if test results come 'out of the blue' (as can happen in prenatal genetic screening programs, for example), the psychological effects may be more pronounced [95].

Risk estimation, communication, recall & perceptions

The complexity of AD etiology poses numerous challenges for risk estimation. The risk estimates provided to REVEAL participants were based on well-established AD risk factors including age, sex, family history and *APOE* genotype. Two main sources of information were used: sex- and age-specific incidence curves for first-degree relatives of persons with AD based on published findings from a large-scale epidemiological study [96,97]; and *APOE* genotype-specific odds ratio estimates for each gender and age reported in a meta-analysis of data from more than 50 studies worldwide [20]. However, these estimates were limited by not considering several other potential risk factors for the disease, including other genes, environmental exposures and gene-gene or gene-environment interactions. Participants were therefore notified that risk estimates represented the best available information but did not incorporate other factors that might influence risk in that given individual.

Another challenge was how to address the issue of potentially differing risks across racial and ethnic groups. The REVEAL group struggled with the dilemma of how to handle the fact that several epidemiological studies had shown African-Americans to be at higher risk than Whites (with *APOE* genotype predicting risk in both groups), but that reasons for this difference were not known. This issue was not only scientific, but also ethical given the troubled history of genetic studies involving African-Americans [98]. Focus groups of African-American community members on the benefits and risks of stratifying risk assessments reached consensus that estimates based primarily on data from Whites should not preclude enrolling African-Americans, but population-specific risk curves should be created if feasible. Risk models specific to ethnicity, gender and *APOE* genotype were subsequently developed for the second REVEAL trial such that African-Americans and Whites received differing risk estimates [99].

It is not enough merely to generate risk estimates for a complex disorder; effective means of conveying risk to often innumerate patients must also be developed and employed. A well-established literature on health risk communication suggests the following:

- Use of natural frequencies (and not just percentages) to convey risk [100];

- Use of graphical representations of risk information (e.g., pictograph) to supplement verbal disclosure [101];
- Use of printed take-home materials to reinforce information presented [102];
- Provision of strategies for coping with risk including potential options for risk reduction and resources for further information.

Where possible, GCs in REVEAL employed such techniques. For example, AD risk was disclosed in verbal and written forms, with use of visual aids including risk curves tailored to sex and *APOE* genotype that conveyed risk information up to age 85 years and in comparison to reference groups including persons without a family history of AD [103]. These line graphs also demonstrated risk over time, reinforcing the importance of the age-specific risks associated with *APOE*.

Despite these efforts, a notable number of participants could not recall their lifetime risk information at 6-week follow-up; however, the vast majority knew their *APOE* genotype status. This finding suggests that genotype is more salient to participants than lifetime risk estimates and demonstrates how gist-level health information is often retained as opposed to numeric estimates [104]. To explore the impact of providing a negative test result (no $\epsilon 4$ allele), a subanalysis of 66 women was conducted; all of these women received a 29% lifetime AD risk estimate, but only 36 women with $\epsilon 4$ -test results received their *APOE* genotype (information which did not alter their lifetime risk estimates). Although both groups received an identical numerical lifetime risk estimate, the $\epsilon 4$ - women perceived their risk as lower, reported testing as having a more positive impact, endorsed less strongly the belief that they might develop AD, and reported a greater reduction in anxiety about AD [105]. Related analyses suggested that receiving $\epsilon 4$ - test results tended to lower participants' perceived AD risk, but that $\epsilon 4$ + results did not necessarily elevate them (possibly because most participants entered the study with high perceived risk at baseline) [106]. These findings highlight the powerful effects of genotype information, even when delivered in a multivariable risk assessment. In the second REVEAL trial, an analysis of perceived versus disclosed risks among participants who had correctly recalled their risk information [107] found that perceived risks were significantly higher than those actually disclosed, suggesting an anchoring effect whereby participants remain influenced by their baseline (i.e., pre-test) risk perceptions even in the face of contradictory risk information [102]. Other studies have also shown that people do not necessarily take risk information at face value [108]. This bias may be particularly likely in risk assessment for common, complex diseases such as AD, where many risk factors are unknown or not fully understood, and where patients may be influenced by their own prior emotional experience through family history and/or caregiving activities.

Behavioral impact of risk assessment

Studies have generally found that genetic risk information by itself is insufficient to promote complex behavior changes such as smoking cessation and alteration of dietary and exercise habits [93,94]. However, an emerging body of evidence [109,110] suggests that genetic risk information may enhance patient preferences for biological interventions (e.g., cardiovascular and depression medications) over health behavior changes (e.g., lifestyle change or psychotherapy) when both are viable options [111]. Some evidence of this phenomenon was found in REVEAL, as the most common health behavior change reported by participants was the addition of vitamins or nutritional supplements (often vitamin E), with endorsement more likely among higher-risk than lower-risk participants [112].

Another behavior of interest was insurance purchasing. $\epsilon 4$ + participants were 5.8-times more likely than controls to report LTC insurance changes during the 1-year follow-up [113]. Such a result is not surprising given that AD often results in a need for 24-h care and is a significant

driver of LTC costs. From a policy perspective, these findings suggest the need to address potential genetic discrimination in the insurance market [54]. Concerns regarding genetic discrimination, given that GINA was not in place during the trial, may help explain results from another REVEAL analysis: showing that only 12% of participants disclosed their test results to a health professional [114].

It should be kept in mind that findings from the REVEAL study may not apply to broader segments of the population, given that participants were predominantly of higher socioeconomic status and generally highly motivated to pursue risk information. In addition, behavioral changes were primarily assessed through self-report and only up to 1 year following disclosure; future studies should seek more objective measures of these domains, with longer-term follow-up. Nevertheless, these initial results provide a first look at the potential psychological and behavioral impact of genetic susceptibility testing for AD.

Future directions for risk assessment models & target populations

Alternative service delivery models

While genetic counseling has played a pioneering role in the provision of disease risk information to individuals and family members, there is limited access to this clinical service for growing numbers of patients [115]. Delivering risk information from susceptibility testing may be well within the purview of standard physician–patient communication because risk factors are routinely discussed, and treating genetic risk factors differently has been criticized as ‘genetic exceptionalism’ [116]. Thus, leaders in the genetic testing field called for a model of care emphasizing condensed protocols, increased collaboration with other healthcare professionals, and use of educational media [117,118]. An interactive computer program has been developed for use in genetic counseling programs for breast cancer, with satisfactory patient education and satisfaction outcomes [119].

The second REVEAL trial examined the safety, effectiveness and impact of a condensed clinical risk communication protocol for 280 first-degree relatives of people with AD. The extended protocol developed in REVEAL I was compared against a condensed protocol where one pretest genetic counseling session was replaced with a mailed educational brochure, resulting in fewer sessions and less face-to-face time (mean: 33 vs 76 min) with the study clinician. Results suggest that genetic risk assessment via the condensed protocol is generally as safe and effective as the original extended protocol; participants did not differ by protocol in terms of depression and anxiety symptoms or by rates of risk recall and comprehension at any point in the year-long follow-up period [116]. A notable exception to this pattern of findings was that $\epsilon 4+$ participants in the extended protocol exhibited a higher level of test-specific distress than their $\epsilon 4-$ counterparts at the 6-week follow-up time point (but not at 6 months or 1 year). This finding suggests that pre-test education and counseling may have a modest protective effect for those participants receiving higher-risk results. Analyses of data from the third REVEAL trial will focus on the impact of telephone disclosure of risk information, building upon work from the literature on *BRCA* testing for women at risk of hereditary breast and ovarian cancer [120]. It will also examine the impact of disclosure of pleiotropic disease risks (i.e., AD and coronary artery disease) associated with *APOE* among over 250 adults with and without immediate AD family history.

Mild cognitive impairment

To date, no studies have examined the impact of providing AD risk information to people with MCI. A survey of 448 clinicians working with MCI patients found that they report commonly discussing AD risk with these patients but that practices for doing so varied greatly [71]. Some studies have begun to explore the subjective experience of MCI patients in coping with their

symptoms [12] as well as the psychological impact of receiving a dementia diagnosis; no significant negative short-term effects were found among either patients or caregivers [122]. Future studies should examine the process and impact of providing AD risk assessment to MCI populations, given both the mounting evidence regarding predictors of AD conversion and the active pursuit of pharmacotherapies targeted to this population.

Conclusion

Risk assessment for AD is not typically performed clinically, but several trends suggest it will become of greater interest. These trends include the rising prevalence of AD, increased understanding of risk factors and etiology, the potential for significantly improved treatments and emergence of DTC risk assessment options. Epidemiological and genetic risk assessment approaches could be used for presymptomatic individuals at any point in the adult life course. AD risk for older adults in preclinical phases could be determined by neuroimaging and other biomarker approaches as well as clinical assessment of MCI. Development and provision of risk assessment, however, will involve addressing numerous challenges, including integration of risk information obtained across different levels of analysis, provider and patient education regarding risk communication, and addressing policy and ethical issues raised by the availability of risk information for a common, severe, incurable disease. Given the current level of societal and scientific investment and interest in combating AD, there should be many promising developments in this area.

Future perspective on AD risk assessment

As the renowned physicist Niels Bohr said, “Prediction is very difficult, especially when it’s about the future.” Yet, we can expect risk assessment for AD in upcoming years to differ in important ways from its current state. We can expect significant advances in predictive capabilities as the epidemiology and pathophysiology of AD become better understood. Social epidemiological studies emerged in recent years to identify new behavioral and health history risk factors for AD. As prospective studies accumulate in the literature, risk models for AD may mature to the point where they encompass a wider range of risk factors and perhaps even suffuse into clinical practice. Such models exist for several other common, complex diseases; for example, the online Breast Cancer Risk Assessment Tool based on the Gail model [123, 124] is available to both patients and professionals via the National Cancer Institute website [203]. A starting point in developing a similar tool for AD could be a late-life dementia risk index [125] which accurately categorizes older adults as having low-, moderate- or high-risk of developing dementia within 6 years. The 15-point index includes: age, neuropsychological test performance, body mass index, *APOE* ϵ 4 status, MRI results, cardiovascular factors, fine-motor function and alcohol consumption.

Genomic research in AD is also rapidly maturing. Although one might classify the search for single-gene causes of AD via genome-wide association studies as disappointing, we are beginning to see promising results from other strategies including epigenetics, gene–environment studies, and gene–gene interactions. For example, SNPs at *CLU* or *PICALM* locations have shown significant associations with carriers of *APOE* ϵ 4 and risk of disease [17,23]. In addition, variants in the gene *TOMM40* have been associated with risk for AD among *APOE* ϵ 3 carriers; this finding might be explained by *TOMM40* being adjacent to and in linkage disequilibrium with *APOE*, with their interaction resulting in pathological protein production [24]. A variable-length sequence repeat polymorphism has been identified on *TOMM40* that in a recent study predicted age of onset risk within the next 7 years for older individuals with normal cognition [126]. A prospective, population-based study is underway that seeks to validate the association of *APOE* genotypes and *TOMM40* haplotypes with age

of onset in AD. This suggests the future possibility of multiplex genetic testing (i.e., testing for a panel of genes rather than a single one) not only to estimate AD risk but also age of onset.

More immediately applicable methods of risk assessment may come from other biomarker strategies used in the preclinical stages of AD. ADNI may ultimately identify biomarkers of clinical utility that reliably distinguish normal aging from MCI from clinical AD [127]. Considerable literature on factors predicting conversion from MCI to AD indicates that possession of the *APOE* $\epsilon 4$ allele is associated with more rapid progression [73,128], and several other factors are under investigation, including neuropsychological measures [129], hippocampal volume as shown by structural MRI [130], reduced tempoparietal glucose metabolism as shown by PET scan [129] and levels of $A\beta$ in CSF [132]. Such biomarkers may become more clinically relevant as MCI continues to emerge as a formal diagnostic category; the revised Diagnostic & Statistical Manual of Mental Disorders (DSM-V) will likely include a category corresponding to MCI [69].

Of course, the landscape for any of the aforementioned risk assessment methods would change dramatically should treatment options significantly improve for AD. Given the investments that major research funders (e.g., National Institute on Aging) and leading pharmaceutical companies (over 30 have drugs intended to treat AD in the FDA pipeline) [204] are making in new treatments for AD, such a development may not be far off. Advancement may occur not only in the development of new treatments, but the targeting of existing ones. Preliminary indications in pharmacogenomics research suggest *APOE* might serve as a useful marker when deciding upon and monitoring response to pharmacotherapy for AD. For example, differential treatment response between $\epsilon 4$ carriers and noncarriers has been observed in clinical trials of rosiglitazone and donepezil, respectively [38,133,134]. In the case of rosiglitazone, *APOE* allowed the identification of a potentially responsive subset of participants, thus enabling Phase III trials with patient subpopulations stratified by $\epsilon 4$ status [133,134]. Although the Phase III trial was negative, pharmacogenomic strategies are likely to continue to be explored in AD treatment and prevention trials [135]. Broad support of genomic-based approaches, including from research funders and advocacy groups, will be necessary to accelerate discovery of effective prevention strategies in this area.

Future challenges

Although research on its risk factors is rapidly maturing, we still lack a theory of AD causation that integrates known risk factors; we do not know if such factors are interactive, additive or orthogonal in producing AD risk. As a common, complex disease, AD presents challenges not only in terms of risk estimation, but also risk communication. Healthcare professionals are not always skilled in conveying probabilistic risk information to patients or may not have adequate opportunity to do so, given time pressures of clinic visits [100,102]. In addition, significant proportions of patients lack even basic health literacy and numeracy skills required to comprehend risk information [136]. These challenges become compounded given that many patients likely to be interested in and appropriate for risk assessment may be older adults already evidencing mild cognitive difficulties compromising their ability to process and remember risk information or give informed consent. It will therefore be important to develop risk communication procedures that accommodate these difficulties, as well as tools to precisely measure individuals' decisional capacity regarding AD risk assessment. The MacArthur Capacity Assessment Tool is a validated instrument that could be adapted for use in this context to identify whether cognitive deficits impair decisional abilities to the point where a surrogate should be involved in medical decision making [137]. Such assessments could also take on legal significance if used by clinicians to determine competency to make medical decisions.

Future ethical, legal & social issues

Research on risk factors and biomarkers for AD are routinely communicated to the lay public via the media, and research participants may become more aware of the potential significance of their own individual research results. Investigators typically do not communicate such results to participants, but some legal, policy, and bioethics scholars have asserted a duty of researchers to disclose research results to participants when this information is of potential clinical and/or personal significance [138–142]. Depending on how research policies and legal authorities define this duty, investigators may face the challenging prospect of disclosing individual research results and implications for AD risk.

Another ‘hot topic’ within bioethics is the emergence of DTC genetic risk assessment. The Genetics and Public Policy Center identified 39 companies currently providing such testing, seven of which include AD risk information as part of their services [205]. Several commentators have raised the following concerns about DTC testing: it relies on an inadequate evidence base for risk estimation; its advertising claims overrate its benefits and minimize its risks; in-person genetics education and counseling is not available to help interpret results and address emotional responses; and testing is not always done in CLIA-approved laboratories. A 2007 statement by the American Society of Human Genetics (ASHG) offered a series of specific policy recommendations for DTC genetic testing and called for the federal government to regulate genetic tests and their marketing more rigorously [143]. The available literature suggests that individuals are usually able to cope adequately with genetic risk information, even for severe incurable diseases like AD. It should be noted, however, that DTC companies do not follow procedures that may mitigate against adverse psychological outcomes; these include baseline screening of interested individuals for severe depression or anxiety and in-person disclosure of genetic results from GCs.

Should consumers gain greater access to genetic risk information for AD, whether via DTC testing or other means, important policy issues regarding insurance will be raised. LTC insurance is of particular interest given that GINA does not cover it, and AD is a major driver of nursing home costs. *APOE* has been shown not only to predict development of AD, but also nursing home placement [144]. If *APOE* testing is utilized by a significant number of consumers to inform their LTC insurance purchasing, then insurers may be within their rights to address this adverse selection by increasing premiums or denying coverage based on *APOE* results. Policymakers will then have to decide whether this practice is acceptable and just.

Executive summary

- Alzheimer’s disease (AD) is a major public health concern owing to its increasing prevalence and the growth of the aging population.
- Disclosure of risk for AD is not typically conducted by healthcare professionals but may soon become a more viable practice given future improvements in AD treatment options and understanding of disease etiology.

Risk & protective factors for AD

- Older age, female sex, African–American or Hispanic ethnicity, and lower educational attainment are demographic factors that are associated with increased risk for AD.
- *APOE*, *APP*, *PSEN1* and *PSEN2* are established genetic risk factors for AD. Numerous other susceptibility genes and genetic markers are currently being investigated.

- Vascular and inflammatory factors and diseases may contribute to AD brain pathology.
- Lifestyle factors including exercise, diet, physical and social activity are associated with lower AD risk; while none of these are proven to reduce AD risk, they are often recommended given their potential benefits and low risk of harm.

Methods of risk assessment for AD

- Risk assessment for AD is being developed to improve clinical trials, tailor disease prevention and risk modification strategies and inform later-life planning.
- Possible methods are epidemiology-based risk indices; predictive genetic testing; other biomarkers; and clinical assessment of mild cognitive impairment.
- Predictive genetic testing for AD is now offered by some direct-to-consumer genetic testing companies, but this practice has raised various ethical, legal and policy concerns.

Impact of risk assessment for Huntington's disease

- The experience of providing genetic testing and counseling for Huntington's disease (another fatal, incurable neuropsychiatric condition) may provide lessons for AD risk assessment given that extensive research has been conducted on the process and impact of Huntington's disease testing.

Impact of risk assessment for AD: the REVEAL Study

- The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study, a series of multisite, randomized clinical trials, is the main source of information about the psychological and behavioral impact of AD risk disclosure that incorporates *APOE* genotype status.
- Findings suggest the following: risk disclosure rarely results in significant, lasting adverse psychological effects; *APOE* status alters disease risk perceptions; higher risk individuals more frequently report behavior changes such as long-term care insurance purchases and use of vitamin E.

Conclusion

- The development and provision of AD risk information entails numerous challenges but is supported by societal and scientific investment and interest in combating AD.

Future perspective

- Future AD risk assessment involves challenges in generating and disclosing AD risk; these include understanding interactions among risk factors and addressing provider and patient difficulties in communicating and understanding health risk information.
- Should AD risk be disclosed more commonly, this practice will likely raise ethical, legal and social issues including regulation of direct-to-consumer genetic test companies and addressing potential genetic discrimination by long-term care insurance providers.

Bibliography

Papers of special note have been highlighted as:

- of interest

■ of considerable interest

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 2007;3(3):186–191. [PubMed: 19595937]
2. Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimers Dement* 2009;5(3):234–270. [PubMed: 19426951] . ■ A public health review of epidemiologic statistics, disease impact on caregiving and healthcare costs, and advances in risk factor knowledge, diagnosis and treatment for Alzheimer's disease (AD) and mild cognitive impairment.
3. Neumann PJ, Hammitt JK, Mueller C, et al. Public attitudes about genetic testing for Alzheimer's disease. *Health Aff. (Millwood)* 2001;20(5):252–264. [PubMed: 11558711]
4. Morris JC. Dementia Update 2005. *Alzheimer Dis. Assoc. Disord* 2005;19(2):100–117. [PubMed: 15942329]
5. Offit K. Genomic profiles for disease risk: predictive or premature? *JAMA* 2008;299(11):1353–1355. [PubMed: 18349097]
6. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch. Neurol* 2002;59(11):1737–1746. [PubMed: 12433261]
7. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007;29(1–2):125–132. [PubMed: 17975326]
8. Green RC, Cupples LA, Go R, et al. Risk of dementia among white and African-American relatives of patients with Alzheimer disease. *JAMA* 2002;287(3):329–336. [PubMed: 11790212]
9. Tang MX, Stern Y, Marder K, et al. The *APOE*- ϵ 4 allele and the risk of Alzheimer disease among African-Americans, whites, and Hispanics. *JAMA* 1998;279(10):751–755. [PubMed: 9508150]
10. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994;271(13):1004–1010. [PubMed: 8139057]
11. Evans DA, Hebert LE, Beckett LA, et al. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Arch. Neurol* 1997;54(11):1399–1405. [PubMed: 9362989]
12. Hendrie HC, Murrell J, Gao S, Unverzagt FW, Ogunniyi A, Hall KS. International studies in dementia with particular emphasis on populations of African origin. *Alzheimer Dis. Assoc. Disord* 2006;20 3 Suppl. 2:S42–S46. [PubMed: 16917194]
13. Stern Y. Cognitive reserve. *Neuropsychologia* 2009;47(10):2015–2028. [PubMed: 19467352]
14. Lautenschlager NT, Cupples LA, Rao VS, et al. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? *Neurology* 1996;46(3):641–650. [PubMed: 8618660]
15. Campion D, Dumanchin C, Hannequin D, et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am. J. Hum. Genet* 1999;65(3):664–670. [PubMed: 10441572]
16. Ertekin-Taner N. Genetics of Alzheimer's disease: a centennial review. *Neurol. Clin* 2007;25(3):611–667. [PubMed: 17659183]
17. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease. *Nat. Genet* 2009;41(10):1094–1099. [PubMed: 19734903]
18. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat. Genet* 2007;39(1):17–23. [PubMed: 17192785]
19. Roses AD. On the discovery of the genetic association of Apolipoprotein E genotypes and common late-onset Alzheimer disease. *J. Alzheimers Dis* 2006;9(3 Suppl):361–366. [PubMed: 16914873]
20. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *APOE and Alzheimer Disease Meta Analysis Consortium. JAMA* 1997;278(16):1349–1356. [PubMed: 9343467]
21. Slooter AJ, Cruts M, Kalmijn S, et al. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. *Arch. Neurol* 1998;55(7):964–968. [PubMed: 9678314]

22. Meyer MR, Tschanz JT, Norton MC, et al. *APOE* genotype predicts when – not whether – one is predisposed to develop Alzheimer disease. *Nat. Genet* 1998;19(4):321–322. [PubMed: 9697689]
23. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease. *Nat. Genet* 2009;41(10):1088–1093. [PubMed: 19734902]
24. Roses AD. The medical and economic roles of pipeline pharmacogenetics: Alzheimer's disease as a model of efficacy and HLA-B(*)5701 as a model of safety. *Neuropsychopharmacology* 2009;34(1):6–17. [PubMed: 18923406]
25. Yu CE, Seltman H, Peskind ER, et al. Comprehensive analysis of *APOE* and selected proximate markers for late-onset Alzheimer's disease: patterns of linkage disequilibrium and disease/marker association. *Genomics* 2007;89(6):655–665. [PubMed: 17434289]
26. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. *Arch. Neurol* 2009;66(10):1210–1215. [PubMed: 19822776]
27. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. *JAMA* 2004;292(23):2901–2908. [PubMed: 15598922]
28. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann. Neurol* 2009;66(2):200–208. [PubMed: 19743450]
29. Szekely CA, Thorne JE, Zandi PP, et al. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. *Neuroepidemiology* 2004;23(4):159–169. [PubMed: 15279021]
30. in t' Veld BA, Ruitenberg A, Hofman A, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N. Engl. J. Med* 2001;345(21):1515–1521. [PubMed: 11794217]
31. Martin BK, Szekely C, Brandt J, et al. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. *Arch. Neurol* 2008;65(7):896–905. [PubMed: 18474729]
32. Cole GM, Frautschy SA. Mechanisms of action of non-steroidal anti-inflammatory drugs for the prevention of Alzheimer's disease. *CNS Neurol. Disord. Drug Targets* 9(2):140–148. [PubMed: 20205646]
33. Lee Y, Back JH, Kim J, et al. Systematic review of health behavioral risks and cognitive health in older adults. *Int. Psychogeriatr* 2010;22(2):174–187. [PubMed: 19883522]
34. Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E ε4 magnifies lifestyle risks for dementia: a population-based study. *J. Cell. Mol. Med* 2008;12(6B):2762–2771. [PubMed: 18318693]
35. Solfrizzi V, Frisardi V, Capurso C, et al. Moderate alcohol consumption, apolipoprotein E, and neuroprotection. *Arch. Neurol* 2009;66(4):541–542. [PubMed: 19364947]
36. Panza F, Capurso C, D'Introno A, et al. Alcohol drinking, cognitive functions in older age, predementia, and dementia syndromes. *J. Alzheimers Dis* 2009;17(1):7–31. [PubMed: 19494429]
37. Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am. J. Geriatr. Psych* 2009;17(7):542–555.
38. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N. Engl. J. Med* 2005;352(23):2379–2388. [PubMed: 15829527]
39. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann. Intern. Med* 2006;144(2):73–81. [PubMed: 16418406]
40. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* 2004;3(6):343–353. [PubMed: 15157849]
41. Geda YE, Roberts RO, Knopman DS, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch. Neurol* 2010;67(1):80–86. [PubMed: 20065133]
42. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch. Neurol* 2010;67(1):71–79. [PubMed: 20065132]
43. Krueger KR, Wilson RS, Kamenetsky JM, Barnes LL, Bienias JL, Bennett DA. Social engagement and cognitive function in old age. *Exp. Aging Res* 2009;35(1):45–60. [PubMed: 19173101]
44. Akbaraly TN, Portet F, Fustini S, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. *Neurology* 2009;73(11):854–861. [PubMed: 19752452]

45. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch. Phys. Med. Rehabil* 2004;85(10):1694–1704. [PubMed: 15468033]
46. Karlinsky H, Sadovnick AD, Burgess MM, Langlois S, Hayden MR, Berg JM. Issues in molecular genetic testing of individuals with suspected early-onset familial Alzheimer's disease. *Alzheimer Dis. Assoc. Disord* 1994;8(2):116–125. [PubMed: 8060604]
47. Steinbart EJ, Smith CO, Poorkaj P, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. *Arch. Neurol* 2001;58(11):1828–1831. [PubMed: 11708991]
48. Green RC. Genetic susceptibility testing for Alzheimer's disease: has the moment arrived? *Alzheimers Care Q* 2002;3(3):208–214. • Discusses the ethics, utility and limitations of genetic susceptibility testing for AD using APOE genotyping.
49. Farrer LA, Brin MF, Elsas L, et al. Statement on use of apolipoprotein E testing for Alzheimer disease. *JAMA* 1995;274(20):1627–1629. [PubMed: 7474250]
50. Relkin N. NIA/Alzheimer's Association Working Group. Apolipoprotein E genotyping in Alzheimer's disease. *Lancet* 1996;347:1091–1095. [PubMed: 8602063]
51. Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer's disease: An ethical perspective. *JAMA* 1997;277(10):832–836. [PubMed: 9052715]
52. Couzin J. Genetics. Once shunned, test for Alzheimer's risk headed to market. *Science* 2008;319(5866):1022–1023. [PubMed: 18292309]
53. Ng PC, Murray SS, Levy S, Venter JC. An agenda for personalized medicine. *Nature* 2009;461(7265):724–726. [PubMed: 19812653]
54. Korobkin R, Rajkumar R. The Genetic Information Nondiscrimination Act – a half-step toward risk sharing. *N. Engl. J. Med* 2008;359(4):335–337. [PubMed: 18650511]
55. Macdonald A, Pritchard D. Genetics, Alzheimer's disease, and long-term care insurance. *N. Am. Actuarial J* 2001;52(2):54–78.
56. Macdonald A, Pritchard D. A mathematical model of Alzheimer's disease and the ApoE gene. *ASTIN Bull* 2000;30:69–110.
57. McConnell LM, Koenig BA, Greely HT, Raffin TA. Genetic testing and Alzheimer disease: has the time come? *Nature Med* 1998;5(7):757–759. [PubMed: 9662356]
58. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;9(1):119–128. [PubMed: 20083042]
59. Ward M. Biomarkers for Alzheimer's disease. *Expert Rev. Mol. Diagn* 2007;7(5):635–646. [PubMed: 17892369]
60. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann. Neurol* 2009;65(4):403–413. [PubMed: 19296504]
61. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA* 2009;302(4):385–393. [PubMed: 19622817]
62. Song F, Poljak A, Smythe GA, Sachdev P. Plasma biomarkers for mild cognitive impairment and Alzheimer's disease. *Brain Res. Rev* 2009;61(2):69–80. [PubMed: 19464319]
63. Jagust WJ, Landau SM, Shaw LM, et al. Relationships between biomarkers in aging and dementia. *Neurology* 2009;73(15):1193–1199. [PubMed: 19822868]
64. Rabinovici GD, Furst AJ, O'Neil JP, et al. 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology* 2007;68(15):1205–1212. [PubMed: 17420404]
65. Hampel H, Burger K, Teipel SJ, Bokde AL, Zetterberg H, Blennow K. Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimers Dement* 2008;4(1):38–48. [PubMed: 18631949]
66. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol* 1999;56(3):303–308. [PubMed: 10190820]
67. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J. Intern. Med* 2004;256(3):183–194. [PubMed: 15324362]
68. Graham JE, Ritchie K. Mild cognitive impairment: ethical considerations for nosological flexibility in human kinds. *Philos. Psychiatr. Psychol* 2006;13:31–43.

69. Ashford JW. Screening for memory disorders, dementia, and Alzheimer's disease. *Aging Health* 2008;4:399–432.
70. Mitchell T, Woodward M, Hirose Y. A survey of attitudes of clinicians towards the diagnosis and treatment of mild cognitive impairment in Australia and New Zealand. *Int. Psychogeriatr* 2008;20(1):77–85. [PubMed: 17565765]
71. Roberts JS, Karlawish J, Uhlmann WR, Petersen RC, Green RC. Mild cognitive impairment in clinical care: a survey of neurologists' attitudes and practices. *Neurology*. 2010 (In Press).
72. Roberts JS. Anticipating response to predictive genetic testing for Alzheimer's disease: a survey of first-degree relatives. *Gerontologist* 2000;40(1):43–52. [PubMed: 10750312]
73. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. *Arch. Neurol* 2009;66(12):1447–1455. [PubMed: 20008648] . ■■ Reviews research progress and the risk for AD among persons with mild cognitive impairment, an important population for future AD risk assessment and early intervention.
74. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology* 2008;30(1):58–69. [PubMed: 18259084]
75. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology* 2010;74(3):201–209. [PubMed: 20042704]
76. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971–983. [PubMed: 8458085]
77. Duyao M, Ambrose C, Myers R, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nat. Genet* 1993;4:387–392. [PubMed: 8401587]
78. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington's disease: an update of the literature. *J. Neurol. Neurosurg. Psych* 2000;69:574–578.
79. Hayden MR. Predictive testing for Huntington's disease: the calm after the storm. *Lancet* 2000;356:216–222.
80. Almqvist E, Bloch M, Brinkman R, Craufurd D, Hayden M. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease. *Am. J. Hum. Genet* 1999;64:1293–1304. [PubMed: 10205260]
81. Huggins M, Bloch M, Wiggins S, et al. Predictive testing for Huntington's disease in Canada: Adverse effects and unexpected results in those receiving a decreased risk. *Am. J. Med. Genet* 1992;42:508–515. [PubMed: 1535178]
82. Timman R, Roos R, Maat-Kievit A, Tibben A. Adverse effects of predictive testing for Huntington disease underestimated: long-term effects 7–10 years after the test. *Health Psychology* 2004;23(2): 189–197. [PubMed: 15008664]
83. Green RC, Clarke VC, Thompson NJ, Woodard JL, Letz R. Early detection of Alzheimer disease: methods, markers, and misgivings. *Alzheimer Dis. Assoc. Disord* 1997;11 Suppl. 5:S1–S5. discussion S37–S39. [PubMed: 9348421]
84. Craufurd D, Dodge A, Kerzin-Storarr L, Harris R. Uptake of presymptomatic predictive testing for Huntington's disease. *Lancet* 1989;2(8663):603–605. [PubMed: 2570293]
85. Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green RC. Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: the REVEAL study. *Genet. Med* 2004;6(4):192–196. [PubMed: 15266206]
86. Roberts JS, LaRusse SA, Katzen H, et al. Reasons for seeking genetic susceptibility testing among first-degree relatives of people with Alzheimer disease. *Alzheimer Dis. Assoc. Disord* 2003;17(2): 86–93. [PubMed: 12794385]
87. Roberts JS, Barber M, Brown TM, et al. Who seeks genetic susceptibility testing for Alzheimer's disease? Findings from a multisite, randomized clinical trial. *Genet. Med* 2004;6(4):197–203. [PubMed: 15266207]
88. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington's disease: an update of the literature. *J. Neurol. Neurosurg. Psych* 2000;69(5):574–578.
89. Marteau TM, Croyle RT. The new genetics. Psychological responses to genetic testing. *BMJ* 1998;316(7132):693–696. [PubMed: 9522800]

90. Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997;277(10):832–836. [PubMed: 9052715]
91. Green RC, Roberts JS, Cupples LA, et al. Disclosure of *APOE* genotype for risk of Alzheimer's disease. *N. Engl. J. Med* 2009;361(3):245–254. [PubMed: 19605829] . • Presents results on the psychological impact of *APOE* genotype risk disclosure in a multisite randomized clinical trial.
92. Romero LJ, Garry PJ, Schuyler M, et al. Emotional responses to *APOE* genotype disclosure for Alzheimer disease. *J. Genet. Couns* 2005;14(2):141–150. [PubMed: 15959645]
93. Marteau TM, Lerman C. Genetic risk and behavioural change. *BMJ* 2001;322(7293):1056–1059. [PubMed: 11325776]
94. Heshka JT, Palleschi C, Howley H, Wilson B, Wells PS. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. *Genet. Med* 2008;10(1):19–32. [PubMed: 18197053]
95. Roberts, JS. Genetic testing. In: Mezey, MD., editor. *Encyclopedia of Care of the Elderly*. New York, NY, USA: Springer Publishing; 2001. p. 298-300.
96. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch. Gen. Psychiatry* 1998;55(9):809–815. [PubMed: 9736007]
97. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology* 1998;51(3):728–733. [PubMed: 9748017]
98. Washington, H. *Medical Apartheid: The Dark History of Medical Experimentation on Black Americans*. New York, NY, USA: Doubleday; 2006. Genetic perdition; p. 299-324.
99. Christensen KD, Roberts JS, Royal CD, et al. Incorporating ethnicity into genetic risk assessment for Alzheimer disease: the REVEAL study experience. *Genet. Med* 2008;10(3):207–214. [PubMed: 18344711]
100. Gigerenzer G, Edwards A. Simple tools for understanding risks: from innumeracy to insight. *BMJ* 2003;327(7417):741–744. [PubMed: 14512488]
101. Lipkus IM. Numeric, verbal, and visual formats of conveying health risks: suggested best practices and future recommendations. *Med. Decis. Making* 2007;27(5):696–713. [PubMed: 17873259]
102. Woloshin S, Schwartz LM. How can we help people make sense of medical data? *Eff. Clin. Pract* 1999;2(4):176–183. [PubMed: 10539543] . • Resource on techniques for effectively communicating health risk information.
103. Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Green RC. Genetic risk assessment for adult children of people with Alzheimer's disease: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. *J. Geriatr. Psych. Neurol* 2005;18(4):250–255.. •• Describes the rationale, risk assessment methods and main results from the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study.
104. Eckert SL, Katzen H, Roberts JS, et al. Recall of disclosed apolipoprotein E genotype and lifetime risk estimate for Alzheimer's disease: the REVEAL Study. *Genet. Med* 2006;8(12):746–751. [PubMed: 17172937]
105. LaRusse S, Roberts JS, Marteau TM, et al. Genetic susceptibility testing versus family history-based risk assessment: impact on perceived risk of Alzheimer disease. *Genet. Med* 2005;7(1):48–53. [PubMed: 15654228]
106. Marteau TM, Weinman J. Self-regulation and the behavioural response to DNA risk information: a theoretical analysis and framework for future research. *Social Sci. Med.* (1982) 2006;62(6):1360–1368.
107. Linnenbringer E, Roberts JS, Hiraki S, Cupples LA, Green RC. "I know what you told me, but this is what I think": Perceived risk of Alzheimer's disease among individuals who accurately recall their genetics-based risk estimate. *Genet. Med.* 2010 (In Press).
108. Senay I, Kaphingst KA. Anchoring-and-adjustment bias in communication of disease risk. *Med. Decis. Making* 2009;29(2):193–201. [PubMed: 19279297]
109. Marteau T, Senior V, Humphries SE, et al. Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. *Am. J. Med. Genet. A* 2004;128A(3):285–293. [PubMed: 15216550]

110. Phelan JC, Yang LH, Cruz-Rojas R. Effects of attributing serious mental illnesses to genetic causes on orientations to treatment. *Psychiatr. Serv* 2006;57(3):382–387. [PubMed: 16524997]
111. Senior V, Marteau TM. Causal attributions for raised cholesterol and perceptions of effective risk-reduction: self-regulation strategies for an increased risk of coronary heart disease. *Psychol. Health* 2007;22(6):699–717.
112. Chao S, Roberts JS, Marteau TM, Silliman R, Cupples LA, Green RC. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer Dis. Assoc. Disord* 2008;22(1):94–97. [PubMed: 18317253]
113. Zick CD, Mathews CJ, Roberts JS, Cook-Deegan R, Pokorski RJ, Green RC. Genetic testing for Alzheimer's disease and its impact on insurance purchasing behavior. *Health Aff. (Millwood)* 2005;24(2):483–490. [PubMed: 15757934]
114. Ashida S, Koehly LM, Roberts JS, Chen CA, Hiraki S, Green RC. Disclosing the disclosure: factors associated with communicating the results of genetic susceptibility testing for Alzheimer's disease. *J. Health Comm* 2009;14(8):768–784.
115. Resta RG. Defining and redefining the scope and goals of genetic counseling. *Am. J. Med. Genet* 2006;142C(4):269–275. [PubMed: 16878300]
116. Green RC, Roberts JS, Chen C, et al. Comparing the impact of a condensed vs extended protocol for disclosure of *APOE* to relatives of patients with AD: the REVEAL study. *Alzheimers Dement* 2007;3(3):S184.
117. Guttmacher AE, Jenkins J, Uhlmann WR. Genomic medicine: who will practice it? A call to open arms. *Am. J. Med. Genet* 2001;106(3):216–222. [PubMed: 11778982]
118. Guttmacher AE. Human genetics on the web. *Annu. Rev. Genomics Hum. Genet* 2001;2:213–233. [PubMed: 11701649]
119. Green MJ, Peterson SK, Baker MW, et al. Effect of a computer-based decision aid on knowledge, perceptions, and intentions about genetic testing for breast cancer susceptibility: a randomized controlled trial. *JAMA* 2004;292(4):442–452. [PubMed: 15280342]
120. Schwartz MD, Valdimarsdottir HB, DeMarco TA, et al. Randomized trial of a decision aid for *BRCA1/BRCA2* mutation carriers: impact on measures of decision making and satisfaction. *Health Psychol* 2009;28(1):11–19. [PubMed: 19210013]
121. Lingler JH, Nightingale MC, Erlen JA, et al. Making sense of mild cognitive impairment: a qualitative exploration of the patient's experience. *Gerontologist* 2006;46(6):791–800. [PubMed: 17169934]
122. Carpenter BD, Xiong C, Porensky EK, et al. Reaction to a dementia diagnosis in individuals with Alzheimer's disease and mild cognitive impairment. *J. Am. Geriatr. Soc* 2008;56(3):405–412. [PubMed: 18194228]
123. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J. Natl Can. Inst* 1989;81(24):1879–1886.
124. Gail MH, Costantino JP, Pee D, et al. Projecting individualized absolute invasive breast cancer risk in African-American women. *J. Natl Can. Inst* 2007;99(23):1782–1792.
125. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology* 2009;73(3):173–179. [PubMed: 19439724]
126. Roses AD, Lutz MW, Amrine-Madsen H, et al. A *TOMM40* variable-length polymorphism predicts the age of late-onset Alzheimer's disease. *Pharmacogenomics J.* 2009 DOI:10.1038/tpj.2009.69 (Epub ahead of print).
127. Mueller SG, Weiner MW, Thal LJ, et al. Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement* 2005;1(1):55–66. [PubMed: 17476317]
128. Farlow MR, He Y, Tekin S, Xu J, Lane R, Charles HC. Impact of *APOE* in mild cognitive impairment. *Neurology* 2004;63(10):1898–1901. [PubMed: 15557508]
129. Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y. Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology* 1995;45(5):957–962. [PubMed: 7746414]

130. Jack CR Jr, Lowe VJ, Senjem ML, et al. ^{11}C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain* 2008;131(Pt 3):665–680. [PubMed: 18263627]
131. Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology* 2003;60(8):1374–1377. [PubMed: 12707450]
132. Andreasen N, Blennow K. CSF biomarkers for mild cognitive impairment and early Alzheimer's disease. *Clin. Neurol. Neurosurg* 2005;107(3):165–173. [PubMed: 15823670]
133. Akuffo EL, Davis JB, Fox SM, et al. The discovery and early validation of novel plasma biomarkers in mild-to-moderate Alzheimer's disease patients responding to treatment with rosiglitazone. *Biomarkers* 2008;13(6):618–636. [PubMed: 18830857]
134. Brodbeck J, Balestra ME, Saunders AM, Roses AD, Mahley RW, Huang Y. Rosiglitazone increases dendritic spine density and rescues spine loss caused by apolipoprotein E4 in primary cortical neurons. *Proc. Natl Acad. Sci. USA* 2008;105(4):1343–1346. [PubMed: 18212130]
135. Rabiner EA, Tzimopoulou S, Cunningham V, et al. Effects of 12 months of treatment with the PPAR γ agonist rosiglitazone on brain glucose metabolism in Alzheimer's Disease: A 18F-FDG PET study. *Alzheimers Dement* 2009;5(4):P207.
136. Medicine, Io. Health literacy: A Prescription to End Confusion. Kindig, DA., editor. Washington, DC, USA: Institute of Medicine of the National Academy of Sciences; 2004.
137. Appelbaum, PS.; Grisso, T. The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Sarasota, FL, USA: Professional Resources; 2001.
138. Ravitsky V, Wilfond BS. Disclosing individual genetic results to research participants. *Am. J. Bioethics* 2006;6(6):8–17.
139. Fernandez CV, Kodish E, Weijer C. Informing study participants of research results: an ethical imperative. *IRB* 2003;25(3):12–19. [PubMed: 14569989]
140. Bookman EB, Langehorne AA, Eckfeldt JH, et al. Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *Am. J. Med. Genet. Part A* 2006;140(10):1033–1040. [PubMed: 16575896]
141. National Bioethics Advisory Commission. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Vol. Volume 1. Rockville, MD, USA: NBAC; 1999.
142. World Health Organization Human Genetics Programme. Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services. Geneva, Switzerland: WHO; 1998.
143. Hudson K, Javitt G, Burke W, Byers P. ASHG Statement* on direct-to-consumer genetic testing in the United States. *Obstetrics Gynecology* 2007;110(6):1392–1395. [PubMed: 18055737]
144. Taylor DH Jr, Ostermann J, van Houtven CH, Tulskey JA, Steinhauer K. What length of hospice use maximizes reduction in medical expenditures near death in the US Medicare program? *Social Sci. Med* 2007;65(7):1466–1478.

Websites

201. Alzheimer's Association. Maintain your brain. www.alz.org/we_can_help_brain_health_maintain_your_brain.asp
202. Siteman Cancer Center. Your disease risk. 2007. www.yourdiseaserisk.wustl.edu
203. National Cancer Institute. Breast Cancer Risk Assessment Tool. www.cancer.gov/bcrisktool
204. Sipkoff, M. Alzheimer's drug pipeline is robust, and usage is quickly expanding. *Managed Care Magazine*. 2009. www.managedcaremag.com/archives/0906/0906.alzheimers.html
205. Direct-to-consumer genetic testing companies: Genetics and Public Policy Center. 2009. www.dnapolicy.org/resources/DTCcompanieslist.pdf

Patent

301. US5508167. 1996.

Table 1

Risk and possible protective factors for Alzheimer's disease.

Domain	Risk factors	Possible protective factors
Demographics	Age (over 65 years)*; female sex; African-American or Hispanic	High educational attainment
Genetics and Family history	Affected first-degree relative*; <i>APOE</i> ε4 allele*; deterministic mutations in the genes encoding: <i>APP</i> on chromosome 21*, <i>PSEN1</i> on chromosome 14* and <i>PSEN2</i> on chromosome 1*; mutations in: <i>CLU</i> , <i>PICALM</i> and <i>SORL1</i>	
Vascular and inflammatory	Stroke; Type 2 diabetes; hypertension; obesity	Statins; NSAIDs
Diet	No or heavy alcohol consumption	Fruits, vegetables, fish and whole grains; low fat and cholesterol; low added sugar; antioxidants (e.g., vitamins C and E); omega-3 polyunsaturated fatty acids (e.g., DHA); anti-inflammatory compounds (e.g., curcumin); light-to-moderate alcohol consumption
Physical activity		Regular, moderate exercise
Social characteristics		Cognitively stimulating leisure and mental activity; frequent social engagement; stress reduction

* Established risk factors; all others are considered candidate factors.

APOE: Apolipoprotein E; APP: Amyloid precursor protein; CLU: Clusterin; DHA: Docosahexaenoic acid; NSAID: Non-steroidal anti-inflammatory drug; PICALM: Phosphatidylinositol binding clathrin assembly protein; PSEN1: Presenilin 1; PSEN2: Presenilin 2; SORL1: Sortilin related receptor L1.

Table 2

Methods of risk assessment for Alzheimer's disease.

Type of approach	Target population	Technique(s)	Variables of interest
Epidemiological	Asymptomatic adults	Self-report	Demographics; health history; health behaviors
Genetic testing	Asymptomatic adults	Blood, saliva sample	Variants/mutations in selected genes
Other biomarkers	Older adults in preclinical phases	Neuroimaging; lumbar puncture	Brain structure volumes; proteome features in biological fluids
Clinical assessment	Older adults with mild cognitive impairment	Neuropsychological testing; neurological exam with informant history	Cognitive functioning; history of symptoms