Published in final edited form as:

Prog Neurobiol. 2013 November ; 110: . doi:10.1016/j.pneurobio.2013.02.005.

Genetic susceptibility testing for neurodegenerative diseases: Ethical and practice issues

J. Scott Roberts, PhD and

Department of Health Behavior & Health Education, University of Michigan School of Public Health, 1415 Washington Heights, SPH I Building, Room 3854, Ann Arbor, MI 48109

Wendy R. Uhlmann, MS, CGC

Departments of Internal Medicine and Human Genetics, University of Michigan Medical School, 300 North Ingalls Building 3A03, SPC 5419, Ann Arbor, MI, USA 48109

J. Scott Roberts: jscottr@umich.edu; Wendy R. Uhlmann: wuhlmann@med.umich.edu

Abstract

As the genetics of neurodegenerative disease become better understood, opportunities for genetic susceptibility testing for at-risk individuals will increase. Such testing raises important ethical and practice issues related to test access, informed consent, risk estimation and communication, return of results, and policies to prevent genetic discrimination. The advent of direct-to-consumer genetic susceptibility testing for various neurodegenerative disorders (including Alzheimer's disease, Parkinson's disease, and certain prion diseases) means that ethical and practical challenges must be faced not only in traditional research and clinical settings, but also in broader society. This review addresses several topics relevant to the development and implementation of genetic susceptibility tests across research, clinical, and consumer settings; these include appropriate indications for testing, the implications of different methods for disclosing test results, clinical versus personal utility of risk information, psychological and behavioral responses to test results, testing of minors, genetic discrimination, and ethical dilemmas posed by whole-genome sequencing. We also identify future areas of likely growth in the field, including pharmacogenomics and genetic screening for individuals considering or engaged in activities that pose elevated risk of brain injury (e.g., football players, military personnel). *APOE* gene testing for risk of Alzheimer's disease is used throughout as an instructive case example, drawing upon the authors' experience as investigators in a series of multisite randomized clinical trials that have examined the impact of disclosing *APOE* genotype status to interested individuals (e.g., first-degree relatives, persons with mild cognitive impairment).

Keywords

Genetic testing; risk assessment; apolipoprotein E (*APOE*); ethics; genetic counseling

© 2013 Elsevier Ltd. All rights reserved.

Corresponding author: J. Scott Roberts, PhD, University of Michigan School of Public Health, 1415 Washington Heights, SPH I Building, Room 3854, Ann Arbor, MI 48109, Phone: (734) 936-9854, Fax: (734) 763-7379.

The authors have no conflicts of interest to report.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. INTRODUCTION

Rapid advances in genomics research have expanded possibilities for the use of genetic testing in risk assessment for neurodegenerative diseases. Predictive testing for conditions such as Huntington's disease has been available for more than twenty years, and in recent years we have seen the identification of numerous genes and genetic markers for a host of neurological disorders. These discoveries allow for genetic susceptibility testing, a type of genetic testing that provides less predictive value than testing for typically rare Mendelian conditions, but that may nonetheless be of interest and use to at-risk individuals. Public access to genetic susceptibility testing for numerous disorders has increased with the rise of personal genomics companies, challenging the traditional medical model of genetic testing and counseling. For these and other reasons, a consideration of the ethical and practice issues involved in genetic susceptibility testing for neurodegenerative diseases is in order. We provide in this section a brief overview of selected conditions for which such testing is potentially available.

1.1 Huntington's disease (HD)

Predictive genetic testing for HD, an autosomal dominant inherited condition, has been available since the late 1980s. Clinical guidelines for presymptomatic testing for HD—including extensive pre- and post-test counseling—were established when genetic testing first became available using linkage analysis (Huntington's Disease Society of America, 1989; Went, 1990; World Federation of Neurology Research Group on Huntington's Chorea, 1989) and were updated in the early 1990s after the gene was cloned (Huntington's Disease Society of America, 1994; International Huntington's Association and the World Federation of Neurology Research Group on Huntington's Chorea, 1994). There is a highly sensitive genetic test available given that >99% of affected individuals have a CAG expansion in the *HTT* gene (Huntington's Disease Collaborative Research Group, 1993; Potter et al., 2004) which permits highly accurate risk assessment for at-risk family members of HD patients (Duyao et al., 1993; Huntington's Disease Collaborative Research Group, 1993).

Predictive genetic testing for HD typically involves three in-person clinic visits with a specialist who has genetics expertise (e.g. genetic counselor, clinical geneticist, neurogeneticist): 1) pre-test genetic counseling 2) informed consent and blood draw and 3) results disclosure and post-test counseling. In addition, prior to genetic testing, patients typically meet with a licensed psychotherapist for a session to confirm that they are appropriate candidates for receiving results with potentially dramatic emotional consequences; a neurology evaluation is also recommended but often deferred if the patient is not concerned about current neurological status (and then ordered as a baseline assessment if the patient tests positive). The presence of a support person throughout the testing process is encouraged. The predictive genetic testing guidelines stipulate that pre-test counseling should include information about the clinical and genetic aspects of HD, how testing is done and its limitations, psychological and social implications (e.g. insurance, employment) of genetic test results and availability of supportive resources. The guidelines emphasize the paramount importance of patient autonomy in making this testing decision and stipulate that testing is only available to individuals 18 years and older (Huntington's Disease Society of America, 1994; Huntington's Disease Society of America/United States Huntington's Disease Genetic Testing Group, 2003; International Huntington's Association and the World Federation of Neurology Research Group on Huntington's Chorea, 1994).

1.2 Alzheimer's disease (AD)

As with HD, Alzheimer's disease (AD) sometimes follows an autosomal dominant inheritance pattern, with atypically early age of onset (Campion et al., 1999). To date, three genes have been identified that are implicated in familial AD: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes (Ertekin-Taner, 2007). In families where a gene mutation has been identified, genetic testing and counseling is available according to the model for HD described above. These mutations cause a very small proportion of AD cases, however; much more common is a risk allele within the Apolipoprotein E (*APOE*) gene. *APOE* codes for a plasma protein involved in lipid transport and has three common alleles (2, 3 or 4), with the 4 allele serving as a notable risk factor for AD and 4 homozygotes being at particularly high lifetime risk (Lautenschlager et al., 1996; Farrer et al., 1997). Genotype specific risks have been shown to vary by sex, ethnicity, and age, with the influence of 4 on AD risk appearing to diminish past age 70 (Slooter et al., 1998). Although the presence of the 4 allele(s) is associated with significantly increased risk of AD, it is neither necessary nor sufficient to cause the disease (L. A. Farrer et al., 1997). This limitation in the predictive value of testing, along with a relative lack of treatment and prevention options for AD, has prompted numerous consensus statements against the clinical use of *APOE* testing (e.g., Post et al., 1997), although access to *APOE* information has occurred through both controlled research studies and commercialized direct-to-consumer genetic testing services. Many other possible susceptibility genes for late-onset AD (e.g., *CLU*, *PICALM*, *SORL1*, *TOMM40*) have been identified through genome wide association studies, (Lambert et al., 2009) although the majority of these are associated with very minor increases in risk, and not all findings have been replicated (Bertram et al., 2007; Harold et al., 2009; Lambert et al., 2009; Roses, 2009; Yu et al., 2007).

1.3 Other neurodegenerative conditions

Amyotrophic lateral sclerosis (ALS), Parkinson's disease and prion diseases have a lower prevalence in the general population than AD (Table 1), and most cases are sporadic. Like AD, these conditions do have a familial form with autosomal dominant inheritance. Both ALS and Parkinson's disease can also be inherited as autosomal recessive conditions, and there is an X-linked form of ALS as well. However, known mutations in the currently identified genes that cause these neurodegenerative conditions only account for a minority of familial cases. For example, while several genes have been identified that cause familial ALS, the most common is the hexanucleotide repeat in *C9ORF72*, which accounts for approximately 40% of familial ALS cases (DeJesus-Hernandez et al., 2011; Renton et al., 2011) and 2–20% of sporadic cases (Morris et al., 2012). Although a number of different genes have been identified as risk factors for Parkinson's disease, most are rare with the exception of *PARK2*, which is found in approximately 50% of individuals with autosomal recessive Parkinson's disease (M. Farrer et al., 2001; Foroud et al., 2003; Klein et al., 2000). The prion diseases (e.g., Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia) are all caused by *PRNP* gene mutations; however, they differ with regard to several disease characteristics, including disease course and age of onset of cognitive and motor difficulties.

For all of the above neurodegenerative conditions, with the exception of HD, a gene mutation needs to be identified in an affected individual before an at-risk family member is clinically tested in order to provide informative risk information. Given limitations with today's technological capabilities, in the absence of testing an affected individual, it will not be known if a negative test result is a true negative. Even identifying a gene mutation is not a certain predictor of outcome or age of onset given that these genes can vary in terms of

penetrance and gene expressivity, and because gene-environment interactions can result in significantly differing disease outcomes.

1.4 Scope of paper

To date, one of the more common medical uses of genetic testing for neurodegenerative conditions has assessed for highly penetrant mutations implicated in HD and autosomal dominant forms of AD and related disorders. In these cases, a positive test result means that development of the relevant disease is nearly inevitable, assuming that one lives long enough and does not succumb to competing mortalities. However, given that the ethical and practical issues involved in such forms of predictive testing are well-described elsewhere (e.g., Schneider et al., 2011; Uhlmann, 2006), this paper will focus instead on genetic susceptibility testing for lower penetrance alleles. In our consideration of susceptibility testing for neurodegenerative diseases, we will use *APOE* testing for risk of Alzheimer's disease as a prototypical case in point, drawing upon our experience as investigators in the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study.

REVEAL is a series of four successive multi-site randomized clinical trials that have examined the process and impact of providing *APOE* testing to interested individuals, primarily first-degree relatives (i.e., parents and siblings) of people with AD (Roberts et al., 2005). In these trials, an interdisciplinary research team developed and disclosed AD risk estimates based on *APOE* genotype, family history of AD, and demographic factors; participants have then been followed for up to a year to assess the psychological and behavioral effects of providing this information. Findings from this research program highlight some of the broader challenges faced in risk estimation and communication using genetic susceptibility tests, and they also raise current and future policy issues that will need to be addressed as the use of genetic susceptibility testing for neurodegenerative disease expands in research, clinical, and commercial contexts.

2. PRACTICE ISSUES

2.1 When (and if) should testing be offered?

Historically, genetic susceptibility testing has primarily been offered in health care scenarios where test results could impact medical decisions. Tests have been deemed appropriate only when they possess both clinical validity and utility (Burke, 2002). That is, the test should be reliable, have strong predictive value, and provide risk information that helps guide decisions about medical management and potential prevention and risk reduction options. *APOE* testing has limited predictive value, and there are currently no proven prevention options for AD; for these and other reasons (e.g., potential psychological and social harms), the medical community has recommended against its use (American College of Medical Genetics/American Society of Human Genetics Working Group on APOE and Alzheimer disease, 1995; National Institute on Aging/Alzheimer's Association Working Group, 1996; Post et al., 1997). However, in other cases susceptibility testing could be useful in determining appropriate intervals for screening (e.g. hereditary cancers), or it could help inform decisions about prophylactic medications or procedures that include potential risks or side effects. In such situations, susceptibility testing may be able to provide more refined risk profiles than would be available through traditional assessment options such as family history.

Decisions about whether or not to offer genetic susceptibility testing have traditionally been made by specialists with expertise in genetics. In current practice, an accurate and thorough risk assessment is central to determining whether genetic susceptibility testing is indicated. As AD demonstrates, some neurodegenerative diseases can occur both commonly in the general population and in an autosomal dominant fashion among select subpopulations. To

determine whether the presenting neurodegenerative disease is potentially an inherited condition, a comprehensive family history (i.e., spanning at least three generations) is essential, with early onset cases and/or multiple affected relatives potentially indicative of primary genetic causes. Generally, it is not considered standard of care to offer predictive testing for adult-onset neurodegenerative diseases to asymptomatic patients without a) positive family history of an inherited neurodegenerative disease, and b) an identified gene mutation in an affected family member (HD is an exception here).

The process of ordering genetic testing can be complex and often requires the expertise of a genetics expert (e.g. clinical geneticist, genetic counselor or other specialist) to select the right test and accurately interpret the test results (Uhlmann, 2009). For example, the risk information yielded by genetic susceptibility testing is a “moving target” with rapid advances being made in genetic testing in terms of tests that are offered and our evolving understanding of the complex interplay among genes, environment and behavior. Genetic testing is highly specialized and often there are only a few laboratories in the US that offer testing for a specific genetic condition. Furthermore, different laboratories may offer different tests for the same genetic condition, requiring ordering clinicians to understand test methodologies and their limitations when making decisions regarding test selection. Depending on the test methodology and the laboratory, genetic tests can range in cost from a few hundred to several thousand dollars, with variable insurance coverage of these options. Given the different test methodologies and sensitivities, selecting the proper genetic test and laboratory are critical (Uhlmann, 2009). To aid such decision making, the federally funded Genetic Testing Registry was launched February 2012 in the US; this centralized database includes information about the availability of genetic tests for a given condition, relevant methodologies, and if known, the clinical validity and utility (National Center for Biotechnology Information U.S. National Library of Medicine, n.d.).

The status quo regarding access to genetic susceptibility testing for neurodegenerative and other conditions has been challenged in recent years by the emergence of personal genomics companies that offer direct-to-consumer (DTC) testing for various neurodegenerative diseases. According to Johns Hopkins University’s Genetics and Public Policy Center (GPPC), as of August 2011, there were 13 companies offering consumers access to genetic susceptibility testing for neurodegenerative diseases, with two of these companies requiring that results be released through a physician (Genetics and Public Policy Center Johns Hopkins University Berman Institute of Bioethics, 2011). These disorders include AD (12 companies offering tests), Parkinson’s disease (4), ALS (3), and prion diseases (2). Some companies offer these tests as part of a broad package including tests for hundreds of other conditions, traits, and ancestral markers, while others target their testing product to a particular disease. The tests in question are generally for low penetrance genes and examine single nucleotide polymorphisms that have been identified through genome-wide association studies to arrive at a risk estimate.

The rationale behind this model of providing genetic risk information is rooted in personal autonomy. Proponents of DTC testing claim that current restrictions on genetic susceptibility testing are unduly paternalistic and that people have an inherent right to know more about their own genome if they so desire. They also note that genetic information can have personal utility beyond that of directly informing medical care (e.g., informing advance planning). However, operating under what could be viewed as the precautionary principle, the medical genetics community has raised numerous concerns about provision of genetic testing in this format (e.g., American College of Medical Genetics, 2004; National Society of Genetic Counselors, 2007). As will be discussed in the policy section of this paper, the complexities involved in interpretation of genetic data and the potential harms associated

with disclosure lead many experts to believe that the traditional medical model is still the most appropriate when considering use of susceptibility testing.

2.2 Informed consent

Properly obtaining informed consent for genetic susceptibility testing, as with any other medical procedure, necessitates adequate disclosure of information, including a description of potential benefits, risks, and limitations. This requirement can be a challenge in genetic susceptibility testing for neurodegenerative diseases because such information is often unknown. Future research may allow us to more precisely identify and quantify the likelihood of test benefits and harms, but at present this information is largely speculative. Another challenge to informed consent in this context is that many patients likely to be interested in and appropriate for genetic risk assessment may already be evidencing cognitive difficulties (e.g., in processing and recalling information) that compromise their ability to fully comprehend the test decision. Informed consent also requires decisional abilities such as reasoning and appreciation that could be impaired in those considering susceptibility testing for neurodegenerative conditions. Informed consent procedures should accommodate these difficulties where possible (e.g., altering the way information is presented, engaging a trusted partner to assist the patient in decision making). It may also be helpful to use validated instruments such as the MacArthur Capacity Assessment Tool that could be adapted for use in this context to determine whether decisional abilities are sufficiently impaired such that a surrogate should be involved in medical decision making (Appelbaum and Grisso, 2001). Such assessments may provide legal justification for judgments of competency to make medical decisions. In situations where proxy decision making is required, health professionals should recognize the potential challenges involved. For example, studies suggest that the surrogate decision maker may not always act in accordance with patients' previously expressed wishes and that certain biases (e.g., regarding willingness to participate in clinical research) may affect proxy decisions (see Beattie, 2007, for a review).

2.3 Risk estimation

The complexity of most neurodegenerative conditions poses numerous challenges for estimating disease risk via genetic susceptibility testing. It is often difficult to integrate genetic information with the many other factors that influence disease expression, such as health behaviors, environmental exposures, comorbid conditions, and social determinants of health. In addition, penetrance, variable expressivity, and genotype-phenotype correlations can impact expression of gene mutations, and we are just starting to learn about gene-gene and gene-environment interactions implicated in human diseases. Even when data are available on these factors, sampling biases may limit the generalizability of results. For example, allele frequencies in genes associated with various diseases are known to differ by racial and ethnic groups, but the populations enrolled in studies of disease risk often lack diversity on this dimension (Bustamante et al., 2011). Furthermore, extrapolating from aggregate data to make inferences at the individual level can be problematic.

These challenges do not mean, however, that genetic susceptibility testing for neurodegenerative conditions is necessarily a futile undertaking. In the REVEAL Study, we developed risk estimates for AD based on well-established risk factors including age, sex, family history, and *APOE* genotype. We created sex- and age-specific incidence curves for first-degree relatives of persons with AD based on findings from large-scale genetic epidemiological studies (Gao et al., 1998; Jorm and Jolley, 1998), incorporating *APOE* genotype-specific odds ratio estimates for each gender and age group reported in a meta-analysis of data from more than 50 studies worldwide (L. A. Farrer et al., 1997). REVEAL study clinicians attempted to be transparent about the limitations of risk estimates disclosed

to participants, given that they did not take into account several other potential risk factors for the disease beyond the genetic and demographic factors noted above. Participants were notified that risk estimates represented the best available information but did not incorporate other factors that might influence risk. Another challenge involved creating risk estimates for African Americans, who had been shown in prior research to be at higher risk than whites, for reasons not fully understood. In contemplating whether and how best to incorporate ethnic background into our risk models, we were cognizant of the troubled history within medicine of “geneticizing” health disparities faced by African Americans (Washington, 2006). Community consultation with African Americans via focus group helped inform our ultimate methods for estimating and communicating disease risk across racial and ethnic subgroups (Christensen et al., 2008).

2.4 Communicating about genetic testing

As noted above, clinical geneticists and genetic counselors have traditionally been the health care providers charged with discussing genetic susceptibility testing with patients. Comprehensive genetic counseling provided prior to genetic testing typically includes the following: review of family and medical history information; risk assessment; education about clinical and genetic aspects of conditions; discussion of the benefits, risks, and limitations of genetic testing and the psychological, social (e.g. insurance, employment) and familial implications of test results; discussion of medical and advance planning options based on possible test outcomes; decision support; and linking patients with supportive resources (Uhlmann, 2009). The traditional genetic counseling model for heritable, high penetrance adult-onset disorders typically includes extensive case preparation, comprehensive review of family and medical history information, and pre- and post-test education and counseling. This model may not be appropriate for relatively common neurological diseases with complex inheritance, given dramatic differences in the predictive value of testing, as well as the types and numbers of patients who might require genetic testing services. There are over 2,400 genetic counselors board certified in the US (American Board of Genetic Counseling Inc., 2010), with most of these professionals geographically concentrated in urban areas and working in prenatal, pediatrics, and cancer genetics clinics (American Board of Medical Genetics; National Society of Genetic Counselors, 2012). To meet anticipated increased future demands for genetic susceptibility testing, leaders in the field have called for the development of alternative models of genetic service delivery (Cohen et al., 2012; Institute of Medicine (US) Roundtable on Translating Genomic-Based Research for Health, 2009) and recognized the need for increased involvement of non-genetics health care professionals, use of educational media, and briefer protocols (Guttmacher et al., 2001).

The emergence of genetic susceptibility testing for neurodegenerative diseases may force neurologists and allied health care professionals to assume a greater role in patient education and counseling in this area, which could pose particular challenges. Such 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 (Gigerenzer and Edwards, 2003; Woloshin and Schwartz, 1999). In addition, many patients lack the basic health literacy and numeracy skills required to comprehend risk information (Institute of Medicine, 2004). Fortunately, health risk communication research has suggested numerous strategies for enhancing understanding of risk information generated by genetic susceptibility testing; these include the following: (a) use of natural frequencies (i.e., not only percentages) to communicate risk estimates (Gigerenzer and Edwards, 2003), (b) supplementing verbal disclosure of risk information with graphical representations (e.g., pictograph) (Lipkus, 2007), (c) use of printed take-home education materials to reinforce information presented in person (Woloshin and Schwartz, 1999), and (d) provision of

strategies for coping with risk, such as possible options for risk reduction and resources for additional information and support.

Such techniques were integrated into the aforementioned REVEAL Study. For example, AD risk was disclosed in both verbal and written forms, supplemented by use of visual aids including risk curves tailored to sex and *APOE* genotype that conveyed risk information from birth up to age 85 (Cupples et al., 2004). These line graphs demonstrated cumulative risk over time, reinforcing the importance of the age-specific risks associated with *APOE* that begin to increase around age 65; the graphs also provide comparisons to reference groups including persons without a family history of AD. Even despite these efforts, a notable number of participants did not retain specific pieces of risk information over time (e.g., their lifetime risk estimate). However, the vast majority recalled their *APOE* 4 status up to one year after disclosure, suggesting that a) genotype is more salient to participants than lifetime risk estimates, and b) gist-level health information is more easily retained than specific numeric estimates (Eckert et al., 2006).

Concerns about the harms of genetic susceptibility testing often center on potential misunderstanding of test results. On one hand, it is feared that recipients of positive test results will develop a fatalistic attitude regarding the about the possibility of future disease, which could impact their psychological well-being and willingness to engage in putative risk reduction behaviors. On the other hand, recipients of negative test results could experience false reassurance, which might lead them to ignore preventive measures, as they would be viewed as unnecessary in their particular case. We found no substantive evidence of fatalism among our REVEAL participants, as virtually all participants receiving 4-positive results recognized that this did not necessarily mean they would inevitably develop AD. However, we did find some modest evidence of false reassurance among participants receiving 4-negative results. For example, in our first REVEAL trial, we compared the risk perceptions of women receiving 3/3 test results and a corresponding 29% lifetime risk estimate to a subsample who received an identical 29% lifetime risk estimate but no *APOE* genotype results. The 4-negative women endorsed less strongly the belief that they might develop AD and perceived their risk as substantively lower, to the point where they were rating their risk on average as similar to that of the general population (i.e., seeming to discount their own positive family history by virtue of the 4-negative result) (LaRusse et al., 2005). These findings suggest a disproportionate weighing of genotype information (often referred to as genetic exceptionalism) within a multivariable risk assessment.

2.5 Psychological impact of results

Another concern expressed about genetic susceptibility testing, particularly for incurable and severe disorders like AD, is that psychological harms may result from disclosing positive test results (Post et al., 1997). The primary outcome of the first REVEAL trial was therefore psychological impact of risk assessment, with validated self-report measures of anxiety, depression symptoms and test-related distress administered at six weeks, six months and one year after disclosure. Results showed no difference between those receiving *APOE* 4+ results and a comparison group receiving AD risk estimates but no *APOE* genotype results. These findings suggest that *APOE* testing under carefully controlled circumstances to adult children of persons with AD did not pose significant psychological risks (Green et al., 2009); the results are consistent with the only other published study of the psychological effects of *APOE* disclosure, a prospective longitudinal cohort study of asymptomatic test recipients where no significant adverse emotional reactions to risk information were found beyond one month (Romero et al., 2005). Findings are also consistent with those from extant research on the psychological impact of genetic testing for other adult-onset disorders, including HD. Such studies have suggested that test-related distress is usually transient assuming patients are provided proper pre- and post-test counseling (Meiser and Dunn,

2000). If test results match initial expectations, then even positive results for severe disorders are usually not overwhelming. However, if positive results come “out of the blue”, as may sometimes occur in prenatal testing clinics, then adverse psychological outcomes may be more common (Roberts, 2001). Although much attention is often focused on the potential impact of “bad news” from a positive genetic test result, baseline psychological functioning is often a better predictor of post-test response than the test result itself; this result has been observed in both REVEAL and studies of response to HD testing (Heshka et al., 2008; Meiser and Dunn, 2000).

However, we should be careful to point out that predictive genetic test results for neurodegenerative diseases can sometimes result in notable distress. A worldwide study of adverse psychiatric responses to HD testing in over 4,500 test recipients found that approximately 1% experienced catastrophic events (i.e., attempted or completed suicide, psychiatric hospitalization) following testing, with the vast majority of these cases involving patients who received a positive test result (Almqvist et al., 1999). Even disclosure of negative HD test results can be stressful, as in cases where patients experience “survivor guilt” or regret over irreversible decisions made prior to testing when they had assumed they would develop HD (Huggins et al., 1992). In addition, the impact of testing on people without post-test counseling is unknown because it is considered standard of care to deliver predictive genetic test results within the traditional genetic counseling model described earlier. A study of psychological responses to HD test results suggests that distress levels are higher at 7–10 years post-disclosure than in the 2–3 years immediately following testing, presumably because test recipients are closer to the likely age of disease onset (Timman et al., 2004). So, while adverse psychological responses to both HD and AD testing have generally been less common and severe than initially feared (Hayden, 2000), this does not mean one should not exercise caution and care when offering or pursuing genetic susceptibility testing for neurodegenerative diseases.

2.6 Behavioral impact of results

Behavioral responses prompted by genetic susceptibility testing can be seen both as potential benefits and harms. Proponents of susceptibility testing have expressed hopes that it would promote healthy behaviors to reduce disease risk. This outcome has not generally been found when the behaviors in question are complex, difficult changes such as smoking cessation and improved diet and exercise (Marteau and Lerman, 2001; McBride et al., 2010). However, a few studies (Marteau et al., 2004; Phelan et al., 2006) suggest that genetic susceptibility testing may enhance preferences for biological interventions (e.g., medications) over health behavior changes (e.g., lifestyle change) when both are viable options (Senior and Marteau, 2007). We observed such a phenomenon in REVEAL, where the most common health behavior change reported by participants was the addition of vitamins or nutritional supplements (often vitamin E), even though our education materials noted this was not a proven means of AD risk reduction (Chao et al., 2008). This finding raises potential concerns about the marketing of nutraceuticals that exploit middle- to older aged adults’ concerns about developing dementia. This industry is relatively unregulated and has been criticized as contributing to a broader effort to commercialize “anti-aging” interventions that are of dubious efficacy and rely on unsubstantiated claims in their marketing (Perls, 2004). Given our results, it may be the case that those who learn they are at increased risk for AD may be susceptible to unproven marketing claims about these products’ capacity to enhance cognition.

Another behavior of interest in response to genetic testing is advance planning. Genetic counseling in HD testing often addresses decisions related to life decisions (e.g., marriage, childbearing, career), family caregiving, health care (e.g., advance directives) and insurance. With regard to the latter, we found in the REVEAL study that participants who learned they

were 4-positive were nearly six times more likely than controls to report long-term care (LTC) insurance changes during a one-year period following risk disclosure (Zick et al., 2005). This result reflects the fact that AD often results in a need for inpatient care and accounts for a significant share of overall LTC costs. Depending on the typical age of onset of the disease in question, genetic susceptibility testing for other neurodegenerative diseases could also have ramifications for life and disability insurance decisions. As will be discussed in the policy section, there are now federal laws in place in the US to protect against genetic discrimination by insurers and employers, but these laws are not comprehensive and do not apply across all insurance markets.

3. POLICY ISSUES

3.1 Access to test results

Policies regarding access to genetic susceptibility testing have generally followed the traditional medical model, where experts determine the value and suitability of health-related procedures. According to this model, many genetic tests for neurodegenerative diseases would be inappropriate at present due to limitations in predictive value and clinical utility (i.e., available treatment options), the challenges of conveying accurate risk information, and the potential for psychological and social harms to individuals receiving risk information. Several consensus statements against *APOE* testing, dating from the mid-1990s, reflect this view (American College of Medical Genetics/American Society of Human Genetics Working Group on *APOE* and Alzheimer disease, 1995; National Institute on Aging/Alzheimer's Association Working Group, 1996; Post et al., 1997). The most recent statement issued by the American College of Medical Genetics and National Society of Genetic Counselors recommended against most uses of *APOE* testing, although it noted that in certain cases "testing may be considered at the clinician's discretion" (Goldman et al., 2011).

Most practicing neurologists adhere to these guidelines, and no insurance companies reimburse for the costs of *APOE* testing in asymptomatic individuals, effectively rendering this type of susceptibility testing inactive in current medical practice. Athena Diagnostics, which owns the patent on *APOE* testing, will not accept clinical samples for *APOE* testing from asymptomatic individuals. Nevertheless, many individuals with a family history of AD are interested in this type of information. Surveys of motivations for pursuing genetic susceptibility testing for AD have suggested that perceived benefits of testing greatly outweigh its perceived limitations and risks, with information viewed as helpful to inform advance planning, encourage monitoring of developments in the field, and assist coping with uncertain risk status (Neumann et al., 2001; Roberts et al., 2003). Respondents have reported in both national surveys and clinical studies that they would be willing to pay significant out-of-pocket costs for susceptibility testing; one national survey found that respondents were willing to pay a mean of nearly \$200 for an AD test of modest predictive value—that is, a positive test would indicate 25% lifetime risk as compared to the general population risk of 10% (Kopits et al., 2011; Neumann et al., 2012). Reflecting a broader trend toward patients asserting their "right to know" personal medical information, many of these interested parties believe they should have access to their personal genetic information and that the decision about whether or not susceptibility testing is appropriate should ultimately be left to them. Until relatively recently, the only way that such individuals could learn their *APOE* status would be to enroll in research studies such as REVEAL. Access to personal genetic information, however, has dramatically expanded in recent years with the development of the field of consumer genomics.

3.2 Consumer genomics

Over the past decade, the capacity for genetic susceptibility testing on a broad scale has emerged. Genome-wide scans for polymorphisms for common, complex conditions can now be conducted at a fraction of their prior cost, using saliva samples that can be shipped from one's home to the company providing the testing service. Test results for numerous diseases at once can be delivered via sophisticated web-based user interfaces that provide relevant and tailored education. Thus, genetic susceptibility testing is now available for a few hundred dollars or less to any individual with access to the Internet, not just patients in specialized genetics clinics or those enrolled in clinical research. A review conducted by the GPPC at Johns Hopkins University in August 2011 identified 27 companies actively providing such testing, 13 of which included risk information for neurodegenerative diseases as part of their services (Genetics and Public Policy Center Johns Hopkins University Berman Institute of Bioethics, 2011). Such companies have received significant attention in both the scientific literature and mass media; for example, in 2008 the journal *Nature* cited "Personal Genomics Goes Mainstream" as a top news story, and in that same year *Time* magazine named "The Retail DNA Test" as its Invention of the Year (Hamilton, 2008; Yeager, 2008).

DTC genetic testing has attracted controversy and raised ethical concerns ever since its inception. Commentators have noted that many company sites claim exaggerated benefits of testing and may not fully disclose risks of testing, particularly privacy and familial implications (Gollust et al., 2003). Such services typically do not screen out psychologically vulnerable consumers or collect detailed family history information, and most do not provide genetic counseling (Hunter et al., 2008), which could increase the potential for inadequate understanding of the meaning or implications of test results. Some commentators have raised concerns that risk information gained from DTC services will lead to more, and potentially unnecessary, health care utilization and screening, raising the risk of psychosocial as well as financial costs (McGuire and Burke, 2008).

Most diseases targeted by DTC companies are complex, encompassing both environmental and multiple genetic risk factors. Thus, risk assessments are currently limited to the provision of low relative risk numbers and cannot accurately predict who will and will not develop disease. Janssens and colleagues (2008) conducted a meta-analysis to examine the clinical validity of the disease profiles offered by a select number of on-line DTC companies and found that many of the gene-disease risks cited by the companies had not been investigated in meta-analyses, or were found to have only modest effects. The authors concluded that "most associations between genetic variants and disease risk are insufficient to support useful applications." In related research, Ng et al. (2009) compared test results from two leading companies for 13 diseases in 5 individuals and found a low level of concordance in disease risk estimates across numerous conditions, suggesting a lack of industry standards in how risk is calculated and conveyed.

As a result of these and other concerns, several laws and regulations have been proposed and enacted for the emerging consumer genetics industry (Javitt et al., 2004). Several states prohibit DTC testing and/or provide restrictions on the type of tests that can be offered (Offit, 2008); for example, some state laws require testing laboratories to be CLIA-approved and to have a physician's order before conducting testing. The American College of Medical Genetics issued a statement in 2004 opposing DTC genetic testing entirely; this statement was then updated in 2008 to assert a minimum set of guidelines for any genetic testing protocol, including DTC services (American College of Medical Genetics, 2008). The National Society of Genetic Counselors (NSGC) adopted a 2007 statement advising patients to proceed with caution when considering DTC services, with a set of nine questions to ask before pursuing such services (National Society of Genetic Counselors, 2007). In 2011,

NSGC updated this statement and emphasized that “unbiased education and counseling” should be provided by a qualified provider. A 2007 statement by the American Society of Human Genetics offered a series of specific policy recommendations for DTC genetic testing: that companies should offer comprehensive and clear information about their tests, that greater provider education is needed, and that the federal government should regulate genetic tests and their marketing more rigorously (Hudson et al., 2007). On the heels of a sharply critical report from the Government Accountability Office (US Government Accountability Office, 2010), the FDA issued “cease and desist” orders against two leading DTC companies, and these regulatory pressures appear to have convinced some companies to move to a testing model where results are only released through a physician.

Advocates of DTC testing counter that many of the presumed harms are merely speculative and that, as the industry matures, it will be able to develop some of the standards and quality control processes that are currently lacking. Proponents cite numerous potential benefits of such testing. For some consumers, pursuing genetic testing directly rather than through health care providers allows greater access to information that some may find difficult to obtain given the relative lack and unequal geographic distribution of specialty genetics service providers. Another potential benefit of DTC testing is that it allows consumers greater control over their genetic information, potentially reducing the threat of genetic discrimination from employers and insurers (although it can also be argued that this threat is often more perceived than real) (Williams-Jones, 2003).

This new model of genetic testing may also provide benefits for education and research. Some companies have developed user interfaces on their websites that provide interactive, engaging education tools that are designed to promote genetic literacy and enhance interest in the topic. Some sites also employ some of the aforementioned recommended practices regarding risk communication, including use of pictographs to represent absolute and relative risks associated with genetic markers. On the research side, one company in particular, 23andMe, has made significant efforts to engage its users in various genetic research projects, including one with particular relevance for Parkinson’s disease. Sergey Brin, the co-founder of Google and husband of 23andMe co-founder Anne Wojcicki, discovered through the testing service that he is a carrier of a LRRK2 mutation that conveys higher risk of PD (his mother, diagnosed with PD in 1999, is also a carrier). This knowledge has prompted Brin to partner with the Parkinson’s Institute and Michael J. Fox Foundation to help create the 23andMe Parkinson’s Genetics Initiative. This project has used the company’s personal genome service as a vehicle for enrolling nearly 10,000 individuals to advance PD research and create an online forum for individuals and families affected by the disease (Goetz, 2010). The project is part of a larger trend in clinical research of using online social networking to engage potential study participants and share information (Cuda-Kroen, 2012). 23andMe has already leveraged their user population to complete and publish a genome-wide association study for PD in a relatively brief timeframe (Do et al., 2011). Data collection is complicated in such studies by relying only on online assessments of research participants (i.e., in-person assessment would be preferable for certain clinical measures). However, given the typically painstaking nature of recruitment for clinical genetics studies in academic research settings, this approach could represent a viable alternative for accelerating the progress of discovery of genetic risk factors for neurodegenerative diseases.

3.3 Testing of minors

The Brin case also raises some ethical concerns, however. For example, the couple has disclosed in interviews that they plan to test their young son to determine his LRRK2 genotype status and associated risk for PD (Pollack, 2009). Other parents interested in learning more about their children’s risk of neurodegenerative diseases could also be able to

access such information via personal genomics services, where regulations against testing of minors without their consent are difficult to enforce. Such decisions would run counter to recommended practices within medical genetics, where children are generally not tested without a specific clinical indication. HD, for example, does have a juvenile onset form with distinct clinical symptoms, which if present would warrant testing in minors. But unless a child is symptomatic for a neurodegenerative disease, as determined by a neurologist, there is no clinical indication to test a child. Different professional organizations have issued policy statements that genetic testing should be deferred until adulthood unless there is medical benefit in childhood from determination of carrier status (American Society of Human Genetics Board of Directors/American College of Medical Genetics Board of Directors, 1995; European Society of Human Genetics, 2009). The predictive genetic testing guidelines for HD make it clear that testing is not available until the individual has reached the age of majority (Huntington's Disease Society of America, 1994; Huntington's Disease Society of America/United States Huntington's Disease Genetic Testing Group, 2003; International Huntington's Association and the World Federation of Neurology Research Group on Huntington's Chorea, 1994).

A main ethical justification for withholding this information is that there are no clinical benefits to outweigh possible harms of receiving distressing and potentially stigmatic information. Some commentators also point to the need to preserve the child's future autonomy in this domain, suggesting that such information violates the child's right to an "open future" and the opportunity to make the testing decision for him- or herself as a competent adult (Davis, 1997). However, others have argued for a less rigid stance against testing of minors for adult-onset conditions, contending that in the absence of proven (as opposed to speculative) harms associated with genetic susceptibility testing, parental authority in such decision-making should be respected (Wilfond and Ross, 2009). This issue may become more prominent if state newborn screening programs begin to incorporate whole-genome sequencing approaches into their efforts (Goldenberg and Sharp, 2012).

3.4 Genetic discrimination

Genetic susceptibility test results have long raised concerns about potential discrimination from insurers and employers. Although proven cases of genetic discrimination are relatively rare, a significant proportion of individuals at-risk for HD have reported perceived discrimination in insurance, employment, health care, and social settings (Bombard et al., 2009). In the US, the federal Genetic Information Nondiscrimination Act (GINA) was passed in 2008, prohibiting health insurers and employers from using genetic information (including family history) to inform decisions about coverage, premiums, or hiring (Korobkin and Rajkumar, 2008). As noted earlier, *APOE* testing may be used by individuals at-risk for AD to help guide decisions about purchasing long-term care insurance. Yet GINA does not cover this type of insurance, meaning that LTC insurers may be within their rights to address potential adverse selection by consumers who know they are at increased risk for AD. Given that AD accounts for a significant proportion of LTC costs, if susceptibility testing becomes more widespread we could ultimately see insurers increase premiums or deny coverage based on *APOE* or other genetic susceptibility test results. This begs the question of whether expansion of GINA protections would be in order to address potential genetic discrimination in LTC, life, and disability insurance domains.

3.5 Return of research results

Genetic research in neurodegenerative diseases has been rapidly expanding for some time now. In recent years, there has been increased focus on the ethical obligations of researchers to disclose individual genetic research results to participants when this information is of potential clinical and/or personal significance. Several prominent national and international

organizations have developed guidelines for researchers regarding a potential duty to inform participants whose genetic research results may have implications for their health and well-being (Fabsitz et al., 2010). Some commentators have suggested that returning of results helps honor the ethical principles of reciprocity and respect for participants and may thereby enhance public trust and willingness to engage in research (Shalowitz and Miller, 2005). However, many issues remain unsettled, including the following: the extent to which research results must be verified (e.g., tested in a CLIA-approved laboratory) before disclosure; a precise definition of clinical significance; and the specific responsibilities of investigators when communicating individual research results to participants (Dressler, 2009). For example, some guidelines specify a need to confirm biological research results by retesting samples before disclosure (National Bioethics Advisory Commission, 1999), while others do not (National Heart Lung and Blood Institute, 2004). An early report from the National Heart, Lung, and Blood Institute (2004) identified a quantitative threshold for disclosure (i.e., a relative risk of disease of 2.0 or higher), but most guidelines frame the significance of findings in more general terms.

Complicating matters is that the methods of genomic research now routinely involve the storage of data in large, international biobanks, with a corresponding reliance on secondary analyses where researchers are far removed from the participants who contributed biological samples (Caulfield et al., 2008). In addition, analyses are increasingly using techniques to interrogate the whole genome, elevating the chances of incidental findings that may need to be considered (Kohane et al., 2006). Given these shifts in the conduct of genomic research, Wolf et al (2012) have developed guidelines for large biobank research systems to discharge potential responsibilities to disclose individual genomic research results to participants (Wolf et al., 2012). Recommendations include proactive identification of results warranting disclosure, incorporation of participant preferences regarding return of results into initial consent processes, and development of processes and procedures whereby primary and secondary researchers communicate about the potential need to return individual research results. Such guidelines are pertinent to several projects where the genomics of neurodegenerative disease are being investigated. AD research, for example, has seen the development of the Alzheimer Disease Neuroimaging Initiative (ADNI), where imaging, genomic (including *APOE* genotype), and cerebrospinal fluid data are collected from older adults with and without AD and mild cognitive impairment (MCI) (Burton, 2011).

4. FUTURE AREAS FOR RESEARCH AND PRACTICE

4.1 Emerging issues

It should be apparent through this discussion that genetic susceptibility testing for neurodegenerative disease is a rapidly evolving area of research and practice. We will likely continue to see scientific advances that provide novel opportunities and present new challenges regarding the clinical application of emerging knowledge. Given current trends, we can expect use of susceptibility testing for neurodegenerative disease to expand over time in particular domains. One prominent area is pharmacogenomics (PGx), where, instead of assessing for disease risk, tests are used to identify differential risk-benefit profiles for patients considering particular medications, including likelihood of side effects. At present, the FDA has included changes to the labels of six medications for neurological conditions, including treatments for HD and ALS (see Table 3). Other genetic markers, including *APOE*, have been associated with differential treatment responses and side effect profiles in a small number of neurology clinical trials, but they are not yet part of clinical practice (Roses, 2009). Provider education in this area will be important to ensure the appropriate application of this emerging technology and to enhance understanding among patients affected by these treatment decisions. Some PGx tests are likely being underutilized because

health care providers lack awareness and comfort with the use and interpretation of these relatively new tests (McCullough et al., 2011).

Genetic tests may also be increasingly used in clinical research to identify appropriate participants for prevention trials with at-risk populations. In AD, there are several secondary prevention trial initiatives in the planning or execution stages to be conducted in asymptomatic individuals selected on the basis of genetic and/or biomarker positivity (Sperling et al., 2011). For example, a \$100 million clinical trial is being launched to test the efficacy of an anti-amyloid agent in individuals who are mutation carriers for genes implicated in dominantly inherited AD (Reiman et al., 2011; Reiman et al., 2010). This public-private partnership will involve recruitment of many younger to middle-aged members of a large extended Colombian family where autosomal dominant AD has affected generations. Such trials necessarily contend with numerous ethical issues regarding whether and how disclose potentially threatening genetic information to a vulnerable population. Many of the participants in the aforementioned trial lack formal education and basic health resources, and some in the research ethics community have suggested a justice-related responsibility of clinical researchers from developed countries to provide ancillary care when conducting clinical trials in underresourced areas (Hyder and Merritt, 2009).

Another area where we can expect significant progress is the development of multivariable risk models for neurodegenerative diseases. Here genetic susceptibility test information would be combined and integrated with other risk factors, including other biomarkers and even behavioral and demographic variables identified through epidemiological studies. For example, a late-life dementia risk index (Barnes et al., 2009) has been developed that categorizes older adults as having low, moderate, or high risk of developing dementia within six years. The index relies on variables representing demographics (age), genetics (*APOE* 4 status), imaging (MRI), functioning (neuropsychological test performance, fine-motor function), and health behaviors and status (body mass index, alcohol consumption). Numerous studies of factors that predict conversion from the amnesic subtype of MCI to AD indicate that *APOE* 4 allele is associated with more rapid progression (Petersen et al., 2009); several other factors are under investigation, including amyloid deposition seen via PET scan and related biomarkers identifiable in CSF (Jack, 2012). Typically, findings from these research assessments are not disclosed in clinical practice to individuals with MCI. However, in the current REVEAL trial, we have developed a protocol for disclosing *APOE* genotype status and related AD risk information to individuals with MCI and their study partners. Participants randomized to the study's intervention arm receive a genetic testing and education protocol that includes risk information based on the participant's age, MCI status, and *APOE* genotype. Here, quantitative estimates for risk of progression to clinical AD within the next three years (range: 8–57%) are communicated to persons with MCI aged 70 and above and their study partners (typically a spouse or adult child), along with information about education and support resources. Participants in the control arm also receive education and AD risk estimates (range: 25–44%), but without the incorporation of genetic test results. Data are being collected on study outcomes including participants' comprehension of risk information, psychological distress, and behavior changes (e.g., advance planning) prompted by test results. Such research can hopefully help inform procedures for integrating genetic and other risk assessments into clinical practice with patients who are already evidencing early signs of neurodegenerative disease but where prognosis is uncertain.

Finally, genetic susceptibility testing for neurodegenerative diseases could ultimately be used to inform decisions beyond medical care, clinical research and insurance. Some studies have suggested that *APOE* 4 carriers are highly prone to dementia following traumatic brain injury, and related studies have identified chronic traumatic encephalopathy (CTE) as

a particular phenotype resulting from repeated traumatic brain injury (DeKosky et al., 2010). This raises the possibility that genetic testing could be used to screen for vulnerability to neurological damage following exposure to high-risk environments such as military combat or even contact sports. Some experts in the field have called for ambitious longitudinal research programs to help explore potential “public health benefits of *APOE* genotyping of high school athletes who intend to participate in impact sports or of prospective military personnel” (Gandy and Dekosky, 2012). If *APOE*-attributable risks can be demonstrated in research studies, these authors contend, then genetic testing may be worth utilizing to inform parents’ and young adults’ decisions about playing football or boxing or engaging in military careers that involve exposure to blast injuries from explosive devices.

4.2 Concluding remarks

At present, much of the activity regarding the genetics of neurodegenerative disease occurs at the basic science level, which is quite understandable given the critical need to understand disease etiology and develop new treatments. However, the implications of these research findings go well beyond the laboratory. The emergence of genetic technologies raises important ethical and practice issues that need to be considered by researchers, clinicians, patients, family members, and policymakers, among others. Given these needs, we recommend a robust portfolio of social and behavioral research that anticipates developments in the field and provides evidence to guide the translation of scientific discoveries into practice. Clinicians and researchers have been understandably reluctant to offer access to genetic susceptibility tests for various neurodegenerative diseases for fear that that results might be misleading or harmful. Moving forward, however, we would advocate going beyond speculation toward well-designed empirical studies that yield an informed view on the likelihood and extent of potential benefits and harms of testing. In the words of Mark Twain, “Supposing is good, but finding out is better.”

Acknowledgments

The authors’ work on this paper was supported by National Institutes of Health grants R01 HG02213 and HG05092. The authors gratefully acknowledge Lan Le, MPH and Natalie Bartnik, BS for their assistance with manuscript preparation.

References

- Almqvist EW, et al. 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(5):1293–1304. [PubMed: 10205260]
- American Board of Genetic Counseling Inc. 2010. Retrieved September 10, 2012, from <http://www.abgc.net/ABGC/AmericanBoardofGeneticCounselors.asp>
- American Board of Medical Genetics. Number of certified specialists in genetics. 2011. Retrieved January 16, 2013, from http://www.abmg.org/pages/resources_certspecial.shtml
- American College of Medical Genetics. ACMG statement on direct-to-consumer genetic testing. 2008. Retrieved from http://www.acmg.net/AM/Template.cfm?Section=Policy_Statements&Template=/CM/ContentDisplay.cfm&ContentID=2975
- American College of Medical Genetics/American Society of Human Genetics Working Group on APOE and Alzheimer disease. Statement on use of apolipoprotein E testing for Alzheimer disease. *J Am Med Assoc.* 1995; 274(20):1627–1629.
- American Society of Human Genetics Board of Directors/American College of Medical Genetics Board of Directors. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet.* 1995; 57(5):1233–1241. [PubMed: 7485175]
- Andersen PM, Al-Chalabi A. Clinical genetics of amyotrophic lateral sclerosis: What do we really know? *Nat Rev Neurol.* 2011; 7(11):603–615. [PubMed: 21989245]

- Appelbaum, PS.; Grisso, T. The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Sarasota, FL: Professional Resource Press; 2001.
- Barnes DE, et al. Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology*. 2009; 73(3):173–179. [PubMed: 19439724]
- Bates, G., et al. Huntington's disease. New York, NY: Oxford University Press; 2002.
- Beattie BL. Consent in Alzheimer's disease research: Risk/benefit factors. *Can J Neurol Sci*. 2007; 34(Suppl 1):S27–31. [PubMed: 17469678]
- Bertram L, et al. Systematic meta-analyses of Alzheimer disease genetic association studies: The AlzGene database. *Nat Genet*. 2007; 39(1):17–23. [PubMed: 17192785]
- Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. *J Clin Invest*. 2005; 115(6):1449–1457. [PubMed: 15931380]
- Bombard Y, et al. Perceptions of genetic discrimination among people at risk for Huntington's disease: A cross sectional survey. *BMJ*. 2009; 338:b2175. [PubMed: 19509425]
- Brickell KL, et al. Early-onset Alzheimer disease in families with late-onset Alzheimer disease: A potential important subtype of familial Alzheimer disease. *Arch Neurol*. 2006; 63(9):1307–1311. [PubMed: 16966510]
- Brown K, Mastrianni JA. The prion diseases. *J Geriatr Psychiatry Neurol*. 2010; 23(4):277–298. [PubMed: 20938044]
- Burke W. Genetic testing. *N Engl J Med*. 2002; 347(23):1867–1875. [PubMed: 12466512]
- Burton A. Big science for a big problem: ADNI enters its second phase. *Lancet Neurol*. 2011; 10(3):206–207. [PubMed: 21349436]
- Bustamante CD, et al. Genomics for the world. *Nature*. 2011; 475(7355):163–165. [PubMed: 21753830]
- Byrne S, et al. Rate of familial amyotrophic lateral sclerosis: A systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2011; 82(6):623–627. [PubMed: 21047878]
- Campion 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]
- Caulfield T, et al. Research ethics recommendations for whole-genome research: consensus statement. *PLoS Biol*. 2008; 6(3)
- Chao S, et al. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL study. *Alzheimer Dis Assoc Disord*. 2008; 22(1):94–97. [PubMed: 18317253]
- Christensen KD, et al. Incorporating ethnicity into genetic risk assessment for Alzheimer disease: The REVEAL study experience. *Genet Med*. 2008; 10(3):207–214. [PubMed: 18344711]
- Cohen SA, et al. Report from the National Society of Genetic Counselors service delivery model task force: a proposal to define models, components, and modes of referral. *J Genet Couns*. 2012; 21(5):645–651. [PubMed: 22566244]
- Cuda-Kroen, G. Search for Parkinson's genes turns to online social networking. 2012. Retrieved from Shots: NPR's Health Blog website: <http://www.npr.org/blogs/health/2012/08/20/158943097/search-for-parkinsons-genes-turns-to-online-social-networking>
- Cupples LA, et al. 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]
- Davis DS. Genetic dilemmas and the child's right to an open future. *The Hastings Center Report*. 1997; 27(2):7–15. [PubMed: 9131346]
- de Rijk MC, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: The EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1997; 62(1):10–15. [PubMed: 9010393]
- DeJesus-Hernandez M, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011; 72(2):245–256. [PubMed: 21944778]
- DeKosky ST, et al. Traumatic brain injury--football, warfare, and long-term effects. *N Engl J Med*. 2010; 363(14):1293–1296. [PubMed: 20879875]

- Do CB, et al. Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. *PLoS Genet.* 2011; 7(6)
- Dressler LG. Disclosure of research results from cancer genomic studies: State of the science. *Clin Cancer Res.* 2009; 15(13):4270–4276. [PubMed: 19549775]
- Duyao M, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nat Genet.* 1993; 4(4):387–392. [PubMed: 8401587]
- Eckert SL, 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]
- Elbaz A, et al. Risk tables for parkinsonism and Parkinson's disease. *J Clin Epidemiol.* 2002; 55(1): 25–31. [PubMed: 11781119]
- Ertekin-Taner N. Genetics of Alzheimer's disease: A centennial review. *Neurol Clin.* 2007; 25(3):611–667. [PubMed: 17659183]
- European Society of Human Genetics. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. *Eur J Hum Genet.* 2009; 17(6):720–721. [PubMed: 19277059]
- Fabsitz RR, et al. Ethical and practical guidelines for reporting genetic research results to study participants: Updated guidelines from a National Heart Lung and Blood Institute Working Group. *Circ: Cardiovasc Genet.* 2010; 3(6):574–580. [PubMed: 21156933]
- Farrer LA, 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. *J Am Med Assoc.* 1997; 278(16):1349–1356.
- Farrer M, et al. Lewy bodies and parkinsonism in families with parkin mutations. *Ann Neurol.* 2001; 50(3):293–300. [PubMed: 11558785]
- Foroud T, et al. Heterozygosity for a mutation in the parkin gene leads to later onset Parkinson disease. *Neurology.* 2003; 60(5):796–801. [PubMed: 12629236]
- Gandy S, Dekosky ST. APOE epsilon4 status and traumatic brain injury on the gridiron or the battlefield. *Sci Transl Med.* 2012; 4(134)
- Gao S, et al. 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]
- Genetics and Public Policy Center Johns Hopkins University Berman Institute of Bioethics. List of DTC genetic testing companies. 2011. Retrieved September 10, 2012, from <http://www.dnapolicy.org/resources/DTCAug2011byDiseasecategory.pdf>
- Gigerenzer G, Edwards A. Simple tools for understanding risks: From innumeracy to insight. *BMJ.* 2003; 327(7417):741–744. [PubMed: 14512488]
- Goetz, T. Sergey Brin's Search for a Parkinson's Cure. *Wired.* 2010. Retrieved from wired.com website: http://www.wired.com/magazine/2010/06/ff_sergeys_search/
- Goldenberg AJ, Sharp RR. The ethical hazards and programmatic challenges of genomic newborn screening. *J Am Med Assoc.* 2012; 307(5):461–462.
- Goldman JS, et al. Genetic counseling and testing for Alzheimer's disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med.* 2011; 13(6):597–605. [PubMed: 21577118]
- Gollust SE, et al. Direct-to-consumer sales of genetic services on the Internet. *Genet Med.* 2003; 5(4): 332–337. [PubMed: 12865763]
- Green RC, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med.* 2009; 361(3):245–254. [PubMed: 19605829]
- Guttmacher AE, et al. Genomic medicine: who will practice it? A call to open arms. *Am J Med Genet.* 2001; 106(3):216–222. [PubMed: 11778982]
- Hamilton, A. Best Inventions of 2008. *Time Magazine.* 2008. Retrieved from Time Lists website: http://www.time.com/time/specials/packages/article/0,28804,1852747_1854493,00.html
- Harold D, 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]

- Hayden MR. Predictive testing for Huntington's disease: The calm after the storm. *Lancet*. 2000; 356(9246):1944–1945. [PubMed: 11130517]
- Heshka JT, et al. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. *Genet Med*. 2008; 10(1):19–32. [PubMed: 18197053]
- Holmes C. Genotype and phenotype in Alzheimer's disease. *Br J Psychiatry*. 2002; 180:131–134. [PubMed: 11823322]
- Hudson K, et al. ASHG Statement on direct-to-consumer genetic testing in the United States. *Obstet Gynecol*. 2007; 110(6):1392–1395. [PubMed: 18055737]
- Huggins M, et al. Predictive testing for Huntington disease in Canada: Adverse effects and unexpected results in those receiving a decreased risk. *Am J Med Genet*. 1992; 42(4):508–515. [PubMed: 1535178]
- Hunter DJ, et al. Letting the genome out of the bottle--will we get our wish? *N Engl J Med*. 2008; 358(2):105–107. [PubMed: 18184955]
- Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease. *Cell*. 1993; 72(6):971–983. [PubMed: 8458085]
- Huntington's Disease Society of America. Guidelines for predictive testing for Huntington's disease. New York, NY: Huntington's Disease Society of America; 1989.
- Huntington's Disease Society of America. Genetic testing for Huntington's disease. New York: Huntington's Disease Society of America; 1994.
- Huntington's Disease Society of America/United States Huntington's Disease Genetic Testing Group. Genetic testing for Huntington's disease: It's relevance and implication (revised): Huntington's Disease Society of America. 2003.
- Hyder AA, Merritt MW. Ancillary care for public health research in developing countries. *J Am Med Assoc*. 2009; 302(4):429–431.
- Institute of Medicine. Health literacy: A prescription to end confusion. Washington DC: National Academy of Sciences; 2004.
- Institute of Medicine (US) Roundtable on Translating Genomic-Based Research for Health. Innovations in Service Delivery in the Age of Genomics: Workshop Summary. Washington DC: National Academies Press; 2009.
- International Huntington's Association and the World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *J Med Genet*. 1994; 31(7):555–559. [PubMed: 7966192]
- Jack CR Jr. Alzheimer disease: New concepts on its neurobiology and the clinical role imaging will play. *Radiology*. 2012; 263(2):344–361. [PubMed: 22517954]
- Janssens AC, et al. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. *Am J Hum Genet*. 2008; 82(3):593–599. [PubMed: 18319070]
- Javitt GH, et al. Direct-to-consumer genetic tests, government oversight, and the first amendment: What the government can (and can't) do to protect the public's health. *Oklahoma Law Review*. 2004; 57:251–302. [PubMed: 15658034]
- Jorm AF, Jolley D. The incidence of dementia: A meta-analysis. *Neurology*. 1998; 51(3):728–733. [PubMed: 9748017]
- Juneja T, et al. Prognosis in familial amyotrophic lateral sclerosis: progression and survival in patients with glu100gly and ala4val mutations in Cu,Zn superoxide dismutase. *Neurology*. 1997; 48(1):55–57. [PubMed: 9008494]
- Klein C, et al. Parkin deletions in a family with adult-onset, tremor-dominant parkinsonism: Expanding the phenotype. *Ann Neurol*. 2000; 48(1):65–71. [PubMed: 10894217]
- Kohane IS, et al. The incidentalome: A threat to genomic medicine. *J Am Med Assoc*. 2006; 296(2):212–215.
- Kopits IM, et al. Willingness to pay for genetic testing for Alzheimer's disease: A measure of personal utility. *Genet Test Mol Biomarkers*. 2011; 15(12):871–875. [PubMed: 21749214]

- 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]
- Lambert JC, 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]
- LaRusse S, 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]
- Lautenschlager NT, 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]
- 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]
- Logroscino G, et al. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry*. 2010; 81(4):385–390. [PubMed: 19710046]
- Majounie E, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: A cross-sectional study. *Lancet Neurol*. 2012; 11(4):323–330. [PubMed: 22406228]
- Marteau TM, Lerman C. Genetic risk and behavioural change. *BMJ*. 2001; 322(7293):1056–1059. [PubMed: 11325776]
- Marteau TM, 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]
- McBride CM, et al. The behavioral response to personalized genetic information: Will genetic risk profiles motivate individuals and families to choose more healthful behaviors? *Annu Rev Public Health*. 2010; 31:89–103. [PubMed: 20070198]
- McCullough KB, et al. Assessment of the pharmacogenomics educational needs of pharmacists. *Am J Pharm Educ*. 2011; 75(3):51. [PubMed: 21655405]
- McGuire AL, Burke W. An unwelcome side effect of direct-to-consumer personal genome testing: raiding the medical commons. *J Am Med Assoc*. 2008; 300(22):2669–2671.
- Meiser B, Dunn S. Psychological impact of genetic testing for Huntington's disease: an update of the literature. *J Neurol Neurosurg Psychiatry*. 2000; 69(5):574–578. [PubMed: 11032605]
- Morris HR, et al. Recent advances in the genetics of the ALS-FTLD complex. *Curr Neurol Neurosci Rep*. 2012; 12(3):243–250. [PubMed: 22477152]
- Nance MA, Myers RH. Juvenile onset Huntington's disease--clinical and research perspectives. *Ment Retard Dev Disabil Res Rev*. 2001; 7(3):153–157. [PubMed: 11553930]
- National Bioethics Advisory Commission. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Vol. 1. Rockville, MD: National Bioethics Advisory Commission; 1999.
- National Center for Biotechnology Information U.S. National Library of Medicine. Genetic Testing Registry. n.d. Retrieved September 10, 2012, from <http://www.ncbi.nlm.nih.gov/gtr/>
- National Heart Lung and Blood Institute. NHLBI Working Group on reporting genetic results in research studies meeting summary. Bethesda, MD: National Institutes of Health; 2004.
- National Institute on Aging/Alzheimer's Association Working Group. Apolipoprotein E genotyping in Alzheimer's disease. *Lancet*. 1996; 347(9008):1091–1095. [PubMed: 8602063]
- National Society of Genetic Counselors. Position Statement: Direct to consumer genetic testing (adopted 2007, revised 2011). 2007. Retrieved from <http://www.nsgc.org/Advocacy/PositionStatements/tabid/107/Default.aspx#DTC>
- National Society of Genetic Counselors. Professional Status Survey. 2012. Retrieved September 16, 2012, from <http://www.nsgc.org/Publications/ProfessionalStatusSurvey/tabid/142/Default.aspx>
- Neumann PJ, et al. Willingness-to-pay for predictive tests with no immediate treatment implications: a survey of US residents. *Health Econ*. 2012; 21(3):238–251. [PubMed: 22271512]
- Neumann PJ, et al. Public attitudes about genetic testing for Alzheimer's disease. *Health Aff (Millwood)*. 2001; 20(5):252–264. [PubMed: 11558711]

- Ng PC, et al. An agenda for personalized medicine. *Nature*. 2009; 461(7265):724–726. [PubMed: 19812653]
- Offit K. Genomic profiles for disease risk: Predictive or premature? *J Am Med Assoc*. 2008; 299(11): 1353–1355.
- Payami H, et al. Increased risk of Parkinson's disease in parents and siblings of patients. *Ann Neurol*. 1994; 36(4):659–661. [PubMed: 7605419]
- Perls TT. Anti-aging quackery: Human growth hormone and tricks of the trade--more dangerous than ever. *J Gerontol A Biol Sci Med Sci*. 2004; 59(7):682–691. [PubMed: 15304532]
- Petersen RC, et al. Mild cognitive impairment: Ten years later. *Arch Neurol*. 2009; 66(12):1447–1455. [PubMed: 20008648]
- Phelan JC, et al. Effects of attributing serious mental illnesses to genetic causes on orientations to treatment. *Psychiatr Serv*. 2006; 57(3):382–387. [PubMed: 16524997]
- Pollack, A. Google co-founder backs vast Parkinson's study. *New York Times*. 2009. Retrieved from The New York Times: Business Section website: http://www.nytimes.com/2009/03/12/business/12gene.html?_r=1
- Post SG, et al. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *J Am Med Assoc*. 1997; 277(10):832–836.
- Potter NT, et al. Technical standards and guidelines for Huntington disease testing. *Genet Med*. 2004; 6(1):61–65. [PubMed: 14726813]
- Reiman EM, et al. Alzheimer's Prevention Initiative: A plan to accelerate the evaluation of presymptomatic treatments. *J Alzheimers Dis*. 2011; 26(Suppl 3):321–329. [PubMed: 21971471]
- Reiman EM, et al. Alzheimer's Prevention Initiative: A proposal to evaluate presymptomatic treatments as quickly as possible. *Biomark Med*. 2010; 4(1):3–14. [PubMed: 20383319]
- Renton AE, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011; 72(2):257–268. [PubMed: 21944779]
- Roberts, JS. Genetic testing. In: Mezey, MD., editor. *Encyclopedia of Care of the Elderly*. New York, NY: Springer Publishing; 2001. p. 298-300.
- Roberts JS, et al. Reasons for seeking genetic susceptibility testing among first-degree relatives of people with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2003; 2(17):86–93. [PubMed: 12794385]
- Roberts JS, et al. Genetic risk assessment for adult children of people with Alzheimer's disease. *J Geriatr Psych Neur*. 2005; 18:250–55.
- 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]
- Schneider SA, et al. Genetic testing for neurologic disorders. *Semin Neurol*. 2011; 31(5):542–552. [PubMed: 22266891]
- 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. *Psychology and Health*. 2007; 22(6):699–717.
- Seshadri S, et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke*. 2006; 37(2):345–350. [PubMed: 16397184]
- Shalowitz DI, Miller FG. Disclosing individual results of clinical research: Implications of respect for participants. *J Am Med Assoc*. 2005; 294(6):737–740.
- Slooter AJ, 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]
- Sperling RA, et al. Testing the right target and right drug at the right stage. *Sci Transl Med*. 2011; 3(111):111cm133.
- Testa D, et al. Survival of 793 patients with amyotrophic lateral sclerosis diagnosed over a 28-year period. *Amyotrophic Lateral Scler Other Mot Neuron Disord*. 2004; 5(4):208–212.
- Timman R, et al. Adverse effects of predictive testing for Huntington disease underestimated: Long-term effects 7–10 years after the test. *Health Psychol*. 2004; 23(2):189–197. [PubMed: 15008664]

- Traynor BJ, et al. Incidence and prevalence of ALS in Ireland, 1995–1997: A population-based study. *Neurology*. 1999; 52(3):504–509. [PubMed: 10025778]
- Uhlmann, WR. Ethical Dilemmas. In: Lynch, D., editor. *Neurogenetics: Scientific and Clinical Advances*. New York, NY: Taylor & Francis; 2006. p. 87-106.
- Uhlmann, WR. Thinking It All Through: Case Preparation and Management. In: Uhlmann, WR.; Schuette, JL.; Yashar, BM., editors. *A Guide to Genetic Counseling*. 2. New York, NY: Wiley-Blackwell; 2009. p. 93-131.
- US Food and Drug Administration (FDA). 2012 Table of Pharmacogenomic Biomarkers in Drug Labels. n.d Dec 13. Retrieved January 15, 2013, from <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>
- US Government Accountability Office. Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices (GAO-10-847T). Washington D.C: 2010. Retrieved from <http://gao.gov/products/GAO-10-847T>
- Van Den Eeden SK, et al. Incidence of Parkinson's disease: Variation by age, gender, and race/ethnicity. *Am J Epidemiol*. 2003; 157(11):1015–1022. [PubMed: 12777365]
- Washington, H. *Medical apartheid: The dark history of medical experimentation on black Americans*. New York: Doubleday; 2006. Genetic perdition; p. 299-324.
- Went L. Ethical issues policy statement on Huntington's disease molecular genetics predictive test. International Huntington Association World Federation of Neurology. *J Med Genet*. 1990; 27(1): 34–38. [PubMed: 2137881]
- Wilfond B, Ross LF. From genetics to genomics: Ethics, policy, and parental decision-making. *J Pediatr Psychol*. 2009; 34(6):639–647. [PubMed: 18647793]
- Williams-Jones B. Where there's a web, there's a way: Commercial genetic testing and the Internet. *J Community Genet*. 2003; 6(1):46–57.
- Wolf SM, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet Med*. 2012; 14(4):361–384. [PubMed: 22436882]
- Woloshin S, Schwartz LM. How can we help people make sense of medical data? *Eff Clin Pract*. 1999; 2(4):176–183. [PubMed: 10539543]
- World Federation of Neurology Research Group on Huntington's Chorea. Ethical issues policy statement on Huntington's disease molecular genetics predictive test. *J Neurol Sci*. 1989; 94(1–3):327–332. [PubMed: 2533250]
- Yeager A. News 2008: The year in which. *Nature*. 2008; 456:844–845. Retrieved from nature.com website: <http://www.nature.com/news/2008/081217/full/456844a.html>. 10.1038/456844a
- Yu CE, 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]
- Zick CD, et al. Genetic testing for Alzheimer's disease and its impact on insurance purchasing behavior. *Health Aff (Millwood)*. 2005; 24(2):483–490. [PubMed: 15757934]

Table 1
Overview of neurodegenerative diseases relevant for genetic susceptibility testing

Disease	Typical Age of Onset	Population Risks	Inheritance	DTC Testing Available? ^a	Sources
Alzheimer's Disease	Early-onset: <60 yrs (<5% of cases) Late-onset: >60 yrs	Lifetime risk in general population: 9–17% Lifetime risk in first-degree relatives: 15–30%	Familial: ~15–25% of cases Autosomal dominant: <5% of cases Sporadic: ~75% of cases	YES	Campion, et al., 1999 Bertram and Tanzi, 2005 Brickell et al., 2006 Holmes, 2002 Seshadri et al., 2006
Amnortrophic Lateral Sclerosis	Sporadic mean age: ~ 56 yrs Familial mean age: 46–47 yrs (high penetrance) 58–64 yrs (low penetrance)	General population prevalence: 1–8 per 100,000	Familial: 5% of cases Autosomal dominant Autosomal recessive X-linked C9ORF72 Repeat Expansion: • Familial: ~40% • Sporadic: ~4–8%	YES	Andersen & Al-Chalabi, 2011 Byrne et al., 2011 DeJesus-Hernandez et al., 2011 Junge et al., 1997 Logrosino et al., 2010 Majounie et al., 2012 Rento et al., 2011 Testa et al., 2004 Traynor et al., 1999 Van Es et al., 2008
Huntington's Disease	Juvenile onset: <20 yrs (<7% of cases) Adult-onset mean age: 35–44 yrs	General population prevalence: 1 in 10,000	Autosomal dominant	NO	Bates et al., 2002 Nance and Myers, 2001
Parkinson's Disease	Juvenile onset: <20 yrs Early-onset: <50 yrs Adult-onset: >50 yrs	Lifetime risk in general population: 1–2% Lifetime risk in first-degree relatives: 3–7%	Autosomal dominant Autosomal recessive	YES	de Rijk et al., 1997 Elbaz et al., 2002 Payami et al., 1994 Van Den Eeden et al., 2003
Inherited Prion Diseases	Familial Creutzfeldt-Jakob disease mean age: highly variable (range: 40–90 yrs) Gerstmann-Sträussler-Scheinker syndrome mean age: 30–50 yrs Fatal familial insomnia mean age: 49 yrs (range: 21–65 yrs)	General population incidence: 1 per 1,000,000	Autosomal dominant: 10–15% cases	YES ^b	Brown and Mastrianni, 2010 Chapman et al., 1994 Gambetti et al., 1995 Spudich et al., 1995 Mastrianni and Roos, 2000 Masters et al., 1981 Windl et al., 1999

^aThe Genetics and Public Policy Center, 2011;

^bCreutzfeldt-Jakob disease only

Table 2**Questions to consider regarding clinical use of genetic susceptibility testing for neurodegenerative disease***Patient factors*

- Does the patient have a family history of the condition?
- Does the patient have children, siblings or other at-risk relatives?
- Is the patient already experiencing possible symptoms?
- Is the patient cognitively able to comprehend the information to make an informed decision and understand the results?
- Is the patient psychologically able to cope with test results?
- Does the patient have identified sources of support (e.g. family members, friends) and access to supportive resources?
- Does the patient have desired insurance coverage – health, life, long-term disability, long-term care?

Disease characteristics

- How common is the neurodegenerative disease in question?
- Is the condition typically sporadic or inherited?
- What is the typical inheritance pattern of the disease?
- What is the typical disease course and does this vary by gene mutation?
- Is the patient approaching or beyond the typical age of onset of symptoms?
- Are there options for prevention and surveillance?

Genetic testing and counseling

- Who is the most appropriate clinician to order the genetic testing?
- What is the positive predictive value of the genetic test?
 - What is the significance of having a gene mutation identified – e.g. is there reduced penetrance, variable expressivity, genotype-phenotype correlations?
- Will genetic test results impact a patient's care and management?
- Will genetic test results impact a patient's life decisions?
- Why is the patient seeking genetic testing at this time?
- Does the patient plan to share results with their health care providers (if ordering DTC) and with other family members?
- Has the patient been informed about and provided with supportive resources?

Table 3

Pharmacogenomics in treatment of neurodegenerative diseases

Drug	Use	Biomarker	Label Sections
Carbamazepine	Treatment of seizure disorders, neuropathic pain	HLA-B*1502	Boxed Warning, Warnings and Precautions
Clobazam	Treatment of seizure disorders and anxiety	CYP2C19	Clinical Pharmacology, Dosage and Administration, Use in Specific Populations
Dextromethorphan, Quinidine	Treatment of the pseudobulbar affect (PBA) in ALS, MS	CYP2D6	Clinical Pharmacology, Warnings and Precautions
Galantamine	Treatment of mild-to-moderate dementia of Alzheimer's disease	CYP2D6	Special Populations
Phenytoin	Management of generalized tonic-clonic (grand mal), complex partial seizures; prevention of seizures following head trauma/neurosurgery	HLA-B*1502	Warnings
Tetrabenazine	Treatment of chorea in Huntington's disease	CYP2D6	Dosage and Administration, Warnings, Clinical Pharmacology

Source: FDA website