Published in final edited form as:

Prog Neurobiol. 2013 November ; 110: . doi:10.1016/j.pneurobio.2013.08.003.

A Review of Quality of Life after Predictive Testing for and Earlier Identification of Neurodegenerative Diseases

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Abstract

The past decade has witnessed an explosion of evidence suggesting that many neurodegenerative diseases can be detected years, if not decades, earlier than previously thought. To date, these scientific advances have not provoked any parallel translational or clinical improvements. There is an urgency to capitalize on this momentum so earlier detection of disease can be more readily translated into improved health-related quality of life for families at risk for, or suffering with, neurodegenerative diseases. In this review, we discuss health-related quality of life (HRQOL) measurement in neurodegenerative diseases and the importance of these “patient reported outcomes” for all clinical research. Next, we address HRQOL following early identification or predictive genetic testing in some neurodegenerative diseases: Huntington disease, Alzheimer's disease, Parkinson's disease, Dementia with Lewy bodies, frontotemporal dementia, amyotrophic

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lateral sclerosis, prion diseases, hereditary ataxias, Dentatorubral-pallidoluysian atrophy and Wilson's disease. After a brief report of available direct-to-consumer genetic tests, we address the juxtaposition of earlier disease identification with assumed reluctance towards predictive genetic testing. Forty-one studies examining health related outcomes following predictive genetic testing for neurodegenerative disease suggested that (a) extreme or catastrophic outcomes are rare; (b) consequences commonly include transiently increased anxiety and/or depression; (c) most participants report no regret; (d) many persons report extensive benefits to receiving genetic information; and (e) stigmatization and discrimination for genetic diseases are poorly understood and policy and laws are needed. Caution is appropriate for earlier identification of neurodegenerative diseases but findings suggest further progress is safe, feasible and likely to advance clinical care.

1. Introduction

Predictive genetic testing and molecular genetic diagnosis have taken an ever-increasing role in clinical practice and translational research for the neurodegenerative diseases over the last two decades. The hope underlying genetic advancements is that accurate and early identification of disease or genetic risk will reduce morbidity and mortality through screening, observation, and early treatment or prevention. Up to now, the identification of genes responsible for adult neurodegenerative disorders has helped elucidate molecular mechanisms underlying the etiology and pathogenesis of these disorders (See Figure 1 from (Bertram and Tanzi, 2005)). Such discoveries have begun to impact biomarker development and drug discovery, but have not yet led to improved treatments or prevention. Twenty years after the discovery of the Huntington disease (HD) gene, in the absence of disease-modifying treatments, we felt it was important to reexamine the human reaction to genetic testing – how individuals and families respond to the sometimes life-altering information. In this review, we discuss the current state of health-related quality of life (HRQOL) measurements in neurodegenerative diseases and the importance of these self-report or “patient reported outcomes” for all clinical research. Next, we address HRQOL following predictive genetic testing in some neurodegenerative diseases: Huntington disease (HD), Alzheimer disease (AD), Parkinson's disease (PD), Dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), prion diseases, hereditary ataxias, Dentatorubral-pallidoluysian atrophy (DRPLA) and Wilson's disease. Predictive genetic testing reflects knowledge of location and number of mutations associated with a condition. In some disorders, a mutation will be family specific, limiting the potential for predictive testing to biologic relatives of a person with a known mutation. Furthermore, some neurodegenerative disorders are genetically heterogenous, with rare cases being inherited in an autosomal dominant fashion in which a mutation may or may not be identified within the family (see Table 1 for an overview). After a brief report of available direct-to-consumer genetic tests, we address the juxtaposition of earlier disease identification with assumed reluctance towards predictive genetic testing. The discussion includes directions for research and practice.

1.1 Background

With the advent of amniocentesis in the 1970s came a steady stream of discourse regarding ethical guidelines for disclosure of genetic information and communication of risk (1979; 1983; Powledge and Fletcher, 1979). Developments in genetic testing and increased public awareness of inherited disease stimulated the formation of committees to examine the ethics of health policy worldwide. For example, The United States Secretary of Health and Human Services chartered the Secretary's Advisory Committee on Genetic Testing (SACGT), the Human Fertilisation and Embryology Authority and the Nuffield Council on Bioethics were established in the United Kingdom, and the Australian Health Ethics Committee carried out

public consultation to prepare the National Health and Medical Research Council report on ethical aspects of genetic testing (Parker and Lucassen, 2002).

With the identification of a host of genes responsible for adult-onset neurodegenerative disorders beginning in the early 1990s, ethical discussions had to encompass several additional areas, most notably, prenatal testing for adult-onset diseases, and the possibility of predictive testing of a child or adult for an adult-onset condition. Institutional review boards and individual investigators struggle to find an appropriate analysis of harms and benefits conferred by genetic testing. Efforts to provide fully informed decision making, as well as efforts to diminish potential harms, have resulted in a series of genetic testing guidelines which continue to influence genetic testing practice. Briefly, such guidelines respect the basic ethical principles upon which the healthcare system has been founded, such as (1) respect for autonomy; (2) informed consent; (3) beneficence and non-maleficence; and (4) justice (Beauchamp and Childress, 2009). Admittedly, much of medical practice rests on the historic Hippocratic Oath which emphasizes that physicians “do no harm”. Hesitancy surrounding predictive testing is often secondary to concerns about potential harms. In 2008, the Genetic Information Nondiscrimination Act was enacted as an important recognition of the power of genetic medicine, the injustice of social harms based on genetic factors, and the importance of health care and employment to each individual (2008). The concepts of health, illness, and quality of life hold meanings across disciplinary boundaries (Erwin, 2012). One way to understand the possible benefits or harms of predictive genetic testing is through a study of HRQOL. Below, we review data gathered over the past 30 years and provide a “cost-benefit analysis” of predictive testing for neurodegenerative diseases.

2. HRQOL overview

Expanded definitions of health and functioning, such as that of the World Health Organizations’ (WHO) International Classification of Functioning, Disability and Health (WHO, 2010), have challenged traditional outcomes and encouraged consideration of contextual factors on a person's well-being, in addition to the impact of health. The WHO defines health as a condition of total well-being, inclusive of multiple domains of well-being and not only the lack of disease. WHO has developed the following functioning domains as constituting HRQOL: physical, social, relational, and emotional well-being (Cella, 1995; Perez et al., 2007). While HRQOL has been well-defined and well-studied, quality of life (QOL), a similar term that is often used interchangeably with HRQOL, does not have a consensus definition, and tends to encompass general well-being (Campbell et al., 1976; Patrick and Erickson, 1988). QOL tends to examine a construct that can be either unidimensional (i.e. general well-being or functional status) or multidimensional in nature. Furthermore, QOL measures by definition (or lack thereof) do not utilize a consensus definition. Assessments of QOL range from using a single item that asks specifically about quality of life, to more comprehensive assessments that focus on multiple aspects of quality of life. In an effort to minimize confusion throughout this review, we focus on the evaluation of HRQOL, and review measures of HRQOL that are specific to HD below.

HRQOL assessments are either generic (i.e., appropriate for use across different populations or diseases) or specific (i.e., targeted towards a specific disease). For example, generic measures of HRQOL include assessments such as the SF-36 (Ware et al., 1994), the WHODAS (WHO, 2012), the EQ5D (Rabin et al., 2011), or the SIP (Bergner et al., 1981). These measures have been well-used in a number of different neurodegenerative diseases, but are often criticized for their lack of specificity and insensitivity to change over time. By definition, these measures capture multiple aspects of HRQOL, but are generic; that is, they do not include disease-specific content that are often the target of clinical interventions (e.g., while many of these measures assess physical functioning, none assess chorea, one of the

hallmark symptoms of HD that is often among the primary outcomes in clinical trial interventions in HD).

Both generic and disease-specific HRQOL measures are typically used to help evaluate the effectiveness of clinical trial and intervention research. For example, the United States Food and Drug Administration (2006) highlights the importance of including self-report measures or “patient-reported outcomes” (PROs) as clinical trial endpoints. In clinical trials, a PRO instrument can be used to measure the impact of an intervention on one or more aspects of patients’ health status, ranging from the purely symptomatic (e.g., headache pain) to more complex concepts (e.g., ability to carry out activities of daily living), to extremely complex concepts such as satisfaction with quality of life, which is widely understood to be a multidomain concept with physical, psychological, and social components.

While a number of generic measures exist that capture HRQOL, these measures often lack the sensitivity needed to capture change over time in specific neurological diseases (Tabrizi et al., 2011), and are not sensitive to prodromal disease (Tibben et al., 1993b). As such, there has been an increased focus on utilizing HRQOL measures that can capture both the generic and specific aspects of HRQOL (e.g., described below).

For example, the National Institutes of Health (NIH) convened a series of meetings to chart a “roadmap” for more productive and efficient medical research (Zerhouni, 2005). One of the programs developed to facilitate the re-engineering of clinical research was the Patient-Reported Outcomes Measurement Information System (PROMIS, n.d.). Although a thorough review of these efforts is beyond the scope of this paper, the reader is referred to recent publications of this revolutionary work (Cella et al., 2010b; Cella et al., 2007; Reeve et al., 2007; Riley et al., 2011). This state-of the art comprehensive system is comprised of largely generic item banks for use across chronic disease conditions that measure HRQOL (Cella et al., 2010a). In addition, the National Institute of Neurological Disorders and Stroke funded the development of the Neuro-QOL; Neuro-QOL complements this work with the development of similar item banks with clinical relevance to stroke, Parkinson's disease, multiple sclerosis, child and adult epilepsy, amyotrophic lateral sclerosis, and muscular dystrophy (Cella et al., 2011). These systems allow for cross-disease comparison (generic item banks) and disease-specific sensitivity (disease-specific item banks). Many identical items (i.e., common data elements; CDEs) are used on both PROMIS and Neuro-QOL to allow “linking” between measures, such that a score on one measure (e.g., PROMIS) can be used to estimate a score on another (e.g., Neuro-QOL). Further, these PRO systems utilize computerized adaptive test (CAT) technology, a test method where each individually administered item is uniquely tailored based on the previous test response. CATs allow clinicians and researchers to ascertain a person's level of functioning with minimal items and maximal precision. Validity and reliability estimates for the Neuro-QOL appear excellent with internal consistencies .85 to .97 (see Table 2 for psychometrics of 13 domains) (Cella et al., 2010b). While the Neuro-QOL offers a state-of-the art measurement system for use in the aforementioned five adult neurological conditions, it has only recently been extended to include an HD-specific assessment. The HDQLIFE (currently under development) is a measurement system and research study designed to validate several Neuro-QOL and PROMIS measures in HD, and develop new, HD-specific CATs (targeting chorea, speech and swallowing difficulties and end of life concerns (Carlozzi and Tulsky, 2013)).

In addition to these new measurement systems that utilize CAT-technology, two other HRQOL measures have recently been developed for use in HD. The HD-QOL-I (Clay et al., 2012), an 11-item self-report measure examining three dimensions (motor functioning, psychology and socializing), has acceptable reliability (Cronbach's $\alpha > 0.84$) and internal consistency, as well as satisfactory construct, discriminant, and external validity; this

measure is available in French and Italian, but not in English. In addition, the HD-QOL a 40-item, self-report English measure designed to evaluate six subdomains (cognitive; hopes and worries; services; physical and functional; mood state; and self and vitality) has adequate reliability, stability, and internal consistency, and good unidimensionality, as well as good construct validity (Hocaoglu et al., 2012). Unfortunately, the HD-QOL does not meet typically accepted minimal sample size criteria for neither the EFA (typically ~ 5 people per item analyzed (Bryant and Yarnold, 1995; Everitt, 1975; Gorsuch, 1983)), the RASCH analysis (typically 250 people for definitive results (Linacre, 1994)), nor the DIF analysis (typically 100 people per group needed; (Scott et al., 2010), calling into question the stability of the foundation for this measurement's development. Therefore, although these measures may have potential for assessing HRQOL in HD, more data is needed to determine their utility and sensitivity in this population, especially within the prodromal phase of HD.

Publications with the primary intent to assess HRQOL in neurodegenerative disorders were found for HD (Ho et al., 2009; Ho et al., 2004), PD, MS, motor neuron diseases (McCabe et al., 2009; O'Connor and McCabe, 2011) and ALS (Olsson Ozanne et al., 2011).

Measures of outcome for clinical research and/or clinical trials in neurodegenerative diseases vary widely across, and even within, diseases. In addition, many traditional outcome measures of neurological disease status have been criticized for failing to illustrate the full impact of the disease and for insensitivity to interventional influence. A grave consequence of inadequate outcome measures occurs when intervention alters a component of disease that is not appropriately considered and potential alleviation and/or aggravation of suffering is not considered in therapeutic decision making. As an example, in the assessment of movement disorders, tremor and/or chorea severity have long been emphasized as the primary outcome measure in interventional studies, though the less-used non-motor aspects of these diseases have been shown to impact independence in functioning and HRQOL, sometimes more significantly than the motor symptoms (Chaudhuri et al., 2007; Hamilton et al., 2003; Jain and Goldstein, 2012; Nehl et al., 2004). As a result, a disproportionate emphasis on motor aspects of disease has occurred. Specific phenotypic measures become highly relevant when an interventional compound is hypothesized to impact specific neural circuitry associated with distinct clinical signs/symptoms. All too often, interventional outcomes impact a broad scope of disease aspects, and either a larger number of clinical outcomes are needed or global measures of improvement are utilized. Building a body of evidence in HRQOL will remain elusive unless a "gold standard" is developed and agreed upon and utilized consistently as outcome measures in clinical studies (Westphal et al., 2011).

Several recent studies have emphasized the importance of novel components relevant to specific diseases that were not fully developed in the generic HRQOL tools. For example, various measures of sleep dysfunction have been associated with depression and cognitive impairment in HD (Aziz et al., 2010; Videnovic et al., 2009) and PD (Postuma et al., 2012a; Postuma et al., 2012b), gastrointestinal dysfunction has been emphasized in PD (Cersosimo and Benarroch, 2012), and anticholinergic burden has been shown to impact engagement in activity and patient reported outcomes in various nursing home residents (Kolanowski and Buettner, 2008). In the largest HRQOL study reviewed, 66,193 nursing home residents were examined to determine the best predictors of HRQOL. Findings showed that language, memory and balance problems were the most highly associated with worsened HRQOL (Lam and Wodchis, 2010).

Most relevant to the current review are three papers suggesting that HRQOL may be impacted in neurodegenerative diseases even before the manifestation of disease is evident enough to warrant a clinical diagnosis. Ready and her colleagues conducted qualitative

analyses of semi-structured interviews of persons who had undergone predictive testing for HD and reported that QOL was most heavily influenced by spirituality, interpersonal relationships, witnessing HD in others, employment concerns, and coping strategies in health persons with a gene mutation (Ready et al., 2011). Similarly, Ho and colleagues showed that HD mutation carriers who were not yet diagnosed with HD were as greatly impacted by self, emotional and social relationship issues as those who have been diagnosed with the disease (Ho and Hocaoglu, 2011). Mitchell et al., examined a large group of persons with mild cognitive impairment who did not meet criteria for dementia and reported cognitive challenges impacted QOL domains even when very mild (Mitchell et al., 2010).

A systematic review of 58 QOL studies for patients living with a rare genetic condition was conducted by Cohen and Biesecker (Cohen and Biesecker, 2010). Findings from the review are helpful from the perspective of predictive genetic testing for neurological diseases. Most studies reviewed reported that QOL of affected (diagnosed) patients was significantly worse than their unaffected (but gene mutation-carrying) counterparts (Lickleder et al., 2008). Strikingly, some studies found that asymptomatic participants reported worse QOL than diagnosed fully manifest patients whereas others reported that individuals with genetic conditions experienced better QOL than their healthy peers who were not at any known genetic risk. Several efforts have been made to better understand what factors can contribute to QOL. As expected, many of the studies find that disease-related factors have a negative impact on QOL, and most scales have included disease-specific symptoms, such as tremor/chorea severity for movement disorders, sensory loss for neuropathies, and measures of cognitive decline for dementia syndromes. The next most common component associated with QOL included psychological well-being typically assessed with depression, anxiety and general distress. Other psychosocial factors impacting QOL included illness perceptions, family functioning, and self-esteem. Importantly, some researchers emphasize more broad, long-term assessments such as effects of cumulative life adversity on family functioning, which can have considerable influence on vulnerability and resilience secondary to neurodegenerative disease (Seery et al., 2010; Shrira et al., 2012). Theoretical frameworks for QOL consider coping strategies as significant predictors of QOL. In general, the use of avoidance, distraction, and disengagement techniques are associated with worse QOL and individuals with acceptance, optimism and hopefulness had better QOL. Although the large number of QOL studies found for genetic diseases is heartening, QOL measures are not yet routinely included in (a) clinical trials and/or (b) predictive testing research for most neurodegenerative diseases.

Although specific HRQOL/QOL instruments have not yet been used routinely in the predictive testing literature, the past three decades have been marked by exhaustive consultation and considerable debate among scientists, ethicists, health professionals and families about the ethical standard of care regarding genetic information. One confounding variable is the difference in social support provided by service providers. These services have the potential to mitigate loss of HRQOL from disease onset (Oliver, 1996). Numerous studies have made efforts to measure potential harms secondary to genetic testing although characterizations of “harm” have varied significantly. For the current review, an effort was made to include any publication describing health related outcomes following predictive testing. Articles that did not provide health-related outcomes that might proxy for quality of life were not included. For instance, papers which only described the test results (e.g., gene mutation positive or negative), only provided demographic (gender, age, race), or that limited outcomes to descriptive non-health related information (number completing the test) are not included. Health related outcomes considered include depression, psychological distress, suicidal ideation and action, global well-being, anxiety, aggression, hostility, perceived impact of events, personality characteristics, ambiguity tolerance, spiritual well-being, life orientation, behavioral style, social support, general health, health care service

utilization, self-esteem, uncertainty, hopelessness, general attitudes, quality of life, perceived stigmatization, and discrimination. For the current review, we searched MedLine and PubMed for articles assessing outcomes following genetic testing in neurodegenerative diseases. We located citations in each paper reviewed to expand the search to include all possible references. The majority of publications involve genetic testing for HD, although other neurodegenerative diseases have been studied as well.

3. Huntington disease

Characterized as an inherited disease in its seminal publication over 140 years ago (Huntington, 1872), HD patients, families and professionals have pioneered the fusion of genetics and health care. Genetic testing for HD began with the localization of the gene by linkage analysis 30 years ago (Gusella et al., 1983) and became a standard of care with the discovery of the HD gene 20 years ago (MacDonald et al., 1993). Collaborative worldwide guidelines for predictive and diagnostic testing in HD were written early in the molecular diagnostic era, have often been adopted for use in other diseases, and have recently been revised by an international group of experts (1989; Association, 1994; MacLeod et al., 2012; See, 1994; Went, 1990).

HD research is unrivaled with regards to the sheer number of publications, the number of genetic testing cases studied, the breadth of geography where genetic counseling was reported, and the number of years since genetic testing. Table 3 presents a brief overview of the 28 publications found reporting health related outcomes following predictive genetic testing in HD. Some specific reviews have been published as well (Almqvist et al., 1999; Meiser and Dunn, 2000; Robins Wahlin, 2007; Tibben, 2007). Papers span from 1992 to the present, represent 15 cities across nine countries, range in sample sizes from four to over 2,000, include repeat assessments for up to seven time points, and measure health outcomes from one week to 25 years since predictive genetic testing. In general, no direct catastrophic reactions were reported, there were few differences between the groups who received a negative versus a positive test result, and most differences reported dissipated with time. Briefly, one study reported greater adverse events (such as depressed mood) in mutation carriers (Almqvist et al., 2003), one reported greater hopelessness in mutation carriers (Timman et al., 2004) and two reported a more avoidant coping style in mutation carriers (Decruyenaere et al., 2003) that disappeared by three years in one study (Tibben et al., 1997). Twelve studies reported improvements from baseline assessments in groups receiving a positive gene test as well as those receiving a negative gene test. Improvements were cited in mental health symptoms (Timman et al., 2004; Wiggins et al., 1996), psychological distress (Almqvist et al., 2003), depression and anxiety (Decruyenaere et al., 2003), well-being (Wiggins et al., 1992), coping methods (Licklederer et al., 2008; Timman et al., 2004), attitudes of perceived positive outcomes secondary to having genetic testing (Codori and Brandt, 1994; Taylor and Myers, 1997), decision-making (Tibben et al., 1993a), and relief from uncertainty (Dufrasne et al., 2011). Nine studies reported that health outcomes were equivalent in both groups, irrespective of gene test result. In Australia, 70% of respondents on a survey (n=60) reported that they strongly agreed that it was important to find out their genetic status, with strong agreement that knowing can provide a greater sense of personal control (58%) and help plan one's future (68%), including the decision to procreate (47%). Sixty-eight percent reported feeling 'great benefit' from knowing their test results. Reported benefits included planning for the future, making decisions, active participation in the HD community and advocating for themselves or families at risk for HD. Many individuals found personal meaning and a sense of community from knowledge of genetic information and from the ability to participate in research. Concerns were noted from participants about family members coping with the results (48%), insurance (30%), employment (20%), and

being treated differently (27%). Interestingly, no participants were strongly concerned that the test is not useful as there is no cure for HD (Goh et al., 2013).

Although group differences were rarely significant based on test result, some studies used regression analyses to more directly examine possible predictors of worse outcomes following predictive genetic testing. The overwhelming predictor of poorer outcome measures was pre-test evidence of poor function on the same measures. For instance, post-test assessments of depression, functioning and distress were best predicted by pre-test psychological measures, irrespective of gene test result (Decruyenaere et al., 1999; DudokdeWit et al., 1998; Gargiulo et al., 2009; Lawson et al., 1996). Additional predictors of worse post-test measures included marital and child-bearing status, proximity to motor diagnosis, and gender. None of these predictors were replicated across studies, however, weakening confidence in their importance. One study reported that mutation carriers sought more education about their disease than non-carriers (Taylor and Myers, 1997).

Several studies focused more on the needs of health professionals involved in predictive testing. One study focused on the critical importance of specialized genetic counseling competencies among health professionals involved in predictive testing, to assist patients in developing and utilizing a wide range of coping strategies after their predictive test (Wahlin et al., 1998). Mariotti and colleagues describe the utility of a case conference for the determination of follow up psychological support and counseling (Mariotti et al., 2010). Tassicker and colleagues suggest the evolving understanding of the clinical reliability, specificity, and utility of the gene test requires ongoing review by the practitioner, and revision of guidelines (i.e., reduced penetrance and mutable normal ranges of CAG repeat lengths) (Tassicker et al., 2006). Although the experience accrued over 20 years suggests that genetic information is not harmful and has numerous benefits, this last point is supported by a host of additional studies and case reports. Issues such as intermediate alleles (Semaka et al., 2006), CAG expansions in offspring with increasing parental age and depending on the sex of the parent (Semaka et al., 2010), testing for persons at 25% risk (Benjamin and Lashwood, 2001; Maat-Kievit et al., 1999), gender differences in testing (Taylor, 2005), racial and cultural differences (Tan et al., 2007), time lapse variability between counseling and test results (Scully et al., 2007), interpretation of psychiatric symptoms/signs (Scourfield et al., 1997), lack of awareness in a test candidate of early signs of the disease, non-compliance to the test protocol, and the utility and protocol for giving information on the relationship between age at onset and CAG-repeat (Tibben, 2007), as does the potential for genetic testing results to affect insurance and employment options (and the impact of GINA), all require careful consideration.

The European Huntington Disease Network (EHDN) initiated a review of the guidelines during the World Congress on Huntington's disease in Dresden in 2007. After a lengthy consultation process and a town hall session at the World Congress meeting in Melbourne in 2011, new recommendations for the predictive genetic test in HD were published in 2012 (MacLeod et al., 2012). Even these new guidelines are not without controversy, as some have viewed them as constrained and failing to empower the consumer and enhance privacy. The guidelines will be reviewed every two years in conjunction with the World Congress on Huntington's disease to prospectively allow all members of the HD community to put forward points for consideration. A committee will be appointed on behalf of the chairs of both the International Huntington Association and the World Federation of Neurology HD Research Group. Such recommendations are consistent with several commentaries promoting ongoing research and review of testing guidelines (Evers-Kiebooms et al., 2000). Table 4 provides an abbreviated summary of highlights of the new HD predictive testing guidelines for 2012 (MacLeod et al., 2012).

Uptake of predictive genetic testing for HD has been much lower than expected. Surveys administered prior to the availability of genetic testing suggested that 56-81% of at-risk individuals would take advantage of a predictive test (Evers-Kiebooms et al., 1989; Kessler et al., 1987; Koller and Davenport, 1984; Markel et al., 1987; Mastromauro et al., 1987; Meissen and Berchek, 1988; Tyler and Harper, 1983). Twenty years after genetic testing was made available, uptake remained at 10-20% (Babul et al., 1993; Craufurd et al., 1989; Quaid and Morris, 1993), though some recent reports suggest that uptake is increasing (Sizer et al., 2012). Although many have speculated about the reasons for the reduced numbers pursuing predictive testing for HD, the causes are likely complex and multifaceted. Explanations put forth include preferences towards avoidant coping styles, single-versus-multi payer health care systems, stigmatization, and lack of legal protections for discrimination (Tassicker et al., 2009).

Genetic discrimination is defined as the denial of rights, privileges, or opportunities or other adverse treatment based solely on genetic information (Erwin et al., 2010). The Genetic Information Nondiscrimination Act (GINA) of 2008 defines genetic discrimination in the context of both family history and genetic information, including medical information (2008). GINA has been criticized for offering limited protections against discrimination, illustrating further the impact of social and legal support systems in maintaining QOL (Rothstein, 2007). GINA provides individuals with limited legal protection against genetic discrimination in the areas of employment and health insurance. It does not provide legal recourse for individuals who suffer discrimination in their private relationships or other daily activities (Erwin, 2008). Table 5 summarizes the results of several surveys across a range of genetic conditions and respondents. Rates of genetic discrimination ranged from 11% of genetic counselors reporting knowledge of health insurance discrimination (Hall et al., 2005) to 46.2% of consumer respondents reporting discrimination secondary to genetic information (Erwin et al., 2010). The I-RESPOND-HD (International Responses to Potential Discrimination From individuals at-risk for HD; HG003330) research project included 433 individuals who had tested either positive or negative for the HD mutation as well as untested persons at risk for developing HD due to family history collected from three Australian, two Canadian, and ten U.S. research sites (J. K. Williams et al., 2010). The cumulative results of all persons reporting one or more instances of genetic discrimination showed that 46.2% of individuals at risk for HD experienced some form of unfair treatment. Findings demonstrated a variety of discriminatory experiences classified as falling into the domains of relationships, insurance, employment and transactions (including legal cases and housing rights). Genetic discrimination in the form of insurance was the single most meaningful form of genetic discrimination reported (according to the respondents). These data were gathered between 2005 and 2008, however, just prior to the enactment of GINA in the United States. Canada and Australia have both published concerns about legal protections as well (Lemmens and Miller, 2003; Otlowski, 2007). In addition to discrimination issues, there are issues regarding the sheer complexity of making complaints or seeking redress within the legal system with results revealing a concerning lack of knowledge of formal legal rights, and very poor knowledge of legislation that prevents employers or health insurers from accessing and using their genetic information (Goh et al., in press) (Otlowski et al., 2007; Otlowski, 2007). In summary, discrimination publications are emerging that might be useful to encourage policy and legal protections with regards to genetic information. Further research will be critical for the development of appropriate policy, law and health care environments to allow consumers to derive maximum benefit from the scientific advances of the genomic revolution.

Whereas the emphasis on research outcomes following genetic testing has been on potential negative consequences, positive outcomes, such as benefits, have been reported as well. Many studies have indicated that the primary reason given for genetic testing uptake has

reliably been to decrease uncertainty (Tibben, 2007). Figure 2 shows a breakdown of benefit responses by topic from the I-RESPOND-HD project (Janet K Williams et al., 2010). Knowledge and understanding was the most common benefit cited by all participants. This category includes information and life knowledge, relief from uncertainty, and being able to advocate or educate oneself and others (Bloch et al., 1992; Decruyenaere et al., 2004; Taylor, 2005). For persons pursuing the predictive genetic test, life planning was the next most common benefit addressed. Life planning has included reproduction, work or retirement, finances, insurance, and planning on behalf of their children. For respondents who had not pursued predictive testing, the second most common benefit of being at risk for HD cited was connections with others, referring to satisfaction with family, community and other relationships.

Ample time has elapsed to assure that empirical data is available to examine both short-term and longer-term impact of predictive testing for HD, a neurodegenerative disorder for which there is only symptomatic treatment. The normative principles developed from the experience with HD have proven helpful for other adult-onset autosomal dominant disorders. What makes a genetic test “predictive” is typically a highly penetrant gene that determines a specific disease as an outcome (although the Wilson's disease gene is autosomal recessive in inheritance). As such, predictive genetic testing is for Mendelian disorders. However, most of the common neurodegenerative diseases (Alzheimer's, Parkinson's, ALS) are not single gene, Mendelian disorders. There may be several Mendelian disorders lumped under the same disease heading (e.g., mutations in synuclein or parkin causing “Parkinson's disease” or inherited prion diseases causing AD) (Roberts and Uhlmann, 2013), and other genetic variants that increase the risk of the disease but without directly causing it (e.g., ApoE4 variants in Alzheimer's disease, or the LRRK2G2019S variant in Parkinson's disease), and still other patients with apparently environmental or mixed genetic-environmental etiologies. The application of current HD guidelines for formulating ethical frameworks may fall short in cases that do not involve a single dominant gene.

Arribas-Ayllon provides a comparison in Table 6 which appropriately emphasizes the simple binary interpretation of a dominant gene (for HD) versus the complexities of risk probabilities required for numeric risk in Alzheimer's disease (AD) (Arribas-Ayllon, 2011). Genetic testing for autosomal dominant disorders typically produces good understanding, a high impact of risk perception and low recall error, whereas susceptibility testing can result in poor understanding, high recall error and a limited impact of the genetic testing outcomes. Some of the comparisons made in Table 6, however, may reflect a lack of commensurate examination for the two predictive testing entities. For instance, HD has undergone a significant examination of potential stigmatization/discrimination research whereas other diseases have not yet undergone this scrutiny. Additionally, it is not yet known whether Mendelian disorders are susceptible to lifestyle and/or environmental influence, although there is little reason to deny that possibility, and the age-dependent penetrance of CAG repeat expansions suggest that disease expression must be modified by other genetic factors, environmental influences, or both. It has been demonstrated that HD mouse models do, indeed, demonstrate altered disease trajectories with environmental variations (Benn et al., 2010; Glass et al., 2004; Hockly et al., 2002; Labbadia et al., 2011; Landles et al., 2010; Lazic et al., 2006; Schilling et al., 2004; Spires et al., 2004). Despite these limitations of the Table 6 comparisons, HD is similar to other cerebral degenerative conditions (including AD, FTD, and dementia with Lewy bodies) in that there is a central neuropathology of a “gain of function” in abnormal proteins (huntingtin, beta-amyloid, tau, synuclein), and as such, the extensive research conducted in HD may be a useful “model” in neurodegenerative research in general (Goh and Chiu, 2011). Table 6 is useful for the field to ponder the possible confines of a direct application of HD genetic testing guidelines to other neurodegenerative

diseases with more complex genetic risks. Recent changes to the law and indications from the disabilities literature show the experience of individuals themselves should be considered in the analysis (Patel et al., 2012; Toombs, 1987).

4. Alzheimer's disease

Heritability estimates for AD suggest genetic variations may account for 58%-80% of AD risk. Predicting the development and prognosis of AD is difficult, however, because only a small percentage of cases present with an autosomal dominant transmission pattern and an early disease onset that make genetic testing practical. To date, three causal genes have been identified which together account for less than 2% of AD: amyloid-beta protein precursor (APP) gene on chromosome 21 (Goate et al., 1991), presenilin1 (PSEN1) gene on chromosome 14 (Sherrington et al., 1995), and presenilin 2 (PSEN2) gene on chromosome 1 (Levy-Lahad et al., 1995; Sherrington et al., 1995) (Li et al., 2012). It has been suggested that a DNA diagnosis is attainable in about 70% of families with autosomal dominant AD and a clinical approach to genetic testing is well described (Liddell et al., 2001). The genetic counseling paradigm initially developed for HD has been successfully adapted for use with these family members (Steinbart et al., 2001). Health-related outcome studies of predictive testing for AD are few. One study followed nine persons from three different families at risk for early onset familial AD, FTD or fatal familial insomnia and used the HD genetic testing protocol (Molinuevo et al., 2005). Anxiety increased in some gene carriers, but no significant negative psychological reactions were observed and all participants positively valued the program. Another study reported on 21 persons at risk for familial early onset AD or FTD who requested predictive testing (Steinbart et al., 2001). Seven of the persons were symptomatic and of the remaining 14 asymptomatic persons, 13 reported that predictive testing was beneficial. There were no significant adverse events and no reported discrimination although two persons reported anxiety and one reported depression. Another study followed 18 members of an extended family with identified early onset AD (Lannfelt et al., 1995) who chose to undergo predictive testing. Rather than report on group data, the authors describe three particular cases, two who tested negative and one who tested positive. Although the gene mutation carrier experienced depression, anxiety and suicidal ideation after receiving results, at one year after testing the individual was back to work and coping well. The authors felt that weekly counseling and appropriate education facilitated positive outcomes following predictive testing for AD. Although genetic counseling always recommends a structured counseling schedule, no guidelines specify that sessions need to occur weekly.

To date, there are no long-term outcome studies of predictive genetic testing for AD, for several reasons. First, the percent of AD cases that are due to autosomal dominant genes is estimated to be low (i.e., <5%). Second, the Mendelian AD families may be less well organized (compared with the HD families) so that communication and education regarding who might benefit from predictive testing is not apparent. Finally, the majority of literary and academic publications have emphasized the challenges associated with predictive testing for susceptibility genes (rather than direct gene testing), since over 95% of AD families are not appropriate for autosomal dominant predictive testing for AD. Moreover, as is true with any genetic test, the absence of a specific genetic risk factor does not ensure that an individual has no risk of developing dementia or neurodegenerative disorders since sporadic cases can occur and many genes are not yet identified. A risk spectrum has been proposed for AD, illustrating how the genetic contribution to disease extends from the most extreme genetic form (the mendelian genes ABPP, PSEN1, PSEN2) to cases influenced by genetic susceptibility factors (i.e., APOE), to a less well-defined part of the continuum involving genes of reduced penetrance, to nongenetic risk factors (i.e., head trauma or

protective effects of education; See Figure 3 from Bertram and Tanzi (Bertram and Tanzi, 2005). Further development of such a continuum may prove useful to genetic counseling.

In 1993, the apolipoprotein E (APOE) E4 allele on chromosome 19 was identified, and research suggested that one allele of E4 increased risk by 3% and having two E4 alleles magnified AD risk 15-fold (Roberts et al., 2004). Since that time, over 550 genes have been found that are considered candidates for association with AD risk, with each new gene conferring substantially lower disease risk than APOE (Bertram and Tanzi, 2008). A series of seven conferences have been held over the last decade to consolidate the growing body of genetic research in AD, and to address the clinical utility of genetic testing. Early debate focused on the promise of predictive testing for early intervention and treatment effectiveness (Evans et al., 2001). As depicted in Figure 4, the utility of predictive testing can be adjudicated by the availability and value of an intervention. Figure 4 shows the degree of utility for some diseases ranked by the authors according to how clinically useful genetic testing might be. At one end of the figure is a disease for which a prophylactic surgery is available, whereas the opposing end of the figure is illustrated by predictive testing for AD, which the authors contend is “unethical because no effective prevention is available” (Evans et al., 2001). Such a utilitarian view is consistent with ethical guidelines and helps close the current gap between the ability to predict health outcomes and the ability to prevent, treat or cure deleterious results (Rothstein, 2000). Many arguments have been made against such single treatment-focused guidelines for predictive testing, however, since much of the outcome data suggests value for participants irrespective of available intervention. Although there is a dearth of outcome studies following susceptibility testing, some excellent research has been conducted. The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study, a series of multisite, randomized clinical trials, is the main source of information about the psychological and behavioral impact of AD risk disclosure that incorporates *APOE* genotype status. In general, the REVEAL study suggests that susceptibility risk genetic testing is safe and rarely (if ever) results in significant adverse effects (Green et al., 2009). In addition, receiving knowledge about APOE status can alter disease risk perceptions and has been associated with behavioral changes such as purchase of long-term care insurance and self-administration of vitamin E (Chao et al., 2008). The most significant concern reported from these studies is poor consumer understanding of susceptibility risks and probabilistic knowledge (M. R. Cassidy et al., 2008). Interestingly, in the REVEAL study, only 27% of participants recalled their test results accurately. Future research is needed to develop a standardized protocol for susceptibility testing that maximizes consumer understanding and advances health care preventive practices. Although there have been no known research studies of genetic discrimination for AD, there is an excellent discussion of potential risks of genetic testing on long term care insurance and the role of genetic tests in insurance underwriting (Fogarty, 1999). Consideration of genetic testing should be conducted in light of the recent findings in HD which strongly suggest that many participants experienced significant benefit from predictive testing, even in the absence of treatment (Janet K Williams et al., 2010).

Genetic testing involving APOE is not currently recommended. The limited predictive value of the test, coupled with a general lack of treatment options for AD, as well as the empirical evidence of how poorly people perceive, recall and communicate complex probabilistic risk information (Marteau et al., 2005) prompted several consensus statements cautioning against susceptibility testing in AD (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).

After further consideration and with caution, however, some are again suggesting that susceptibility testing using APOE should be reconsidered as a viable risk assessment option

for three reasons (Roberts and Tersego, 2010). First, knowledge of the etiology of AD is rapidly advancing. Second, preventive clinical trials sponsored by NIH and pharmaceutical companies are already underway. Third, and primarily, private companies are offering genetic risk assessments for AD through direct-to-consumer (DTC) products marketed via the Internet. These factors enhance the pressure on health care practitioners to develop and implement efficient and effective genetic testing protocols for susceptibility testing in AD (see Roberts and Uhlmann, this issue). Several studies suggest interest in genetic testing in AD is very high, even in the absence of treatment. Planning for the future was the most important reason cited, with examples such as arranging personal affairs, preparing family members, doing things earlier than otherwise planned, and relief from uncertainty (Cutler and Hodgson, 2003; Roberts and Tersego, 2010). The practice guidelines of the National Society of Genetic Counselors (NSGC) and the American College of Medical Genetics (ACMG) were developed by members to assist health care providers in making decisions about appropriate management of genetic information in AD. Briefly, the HD guidelines are recommended for predictive testing of asymptomatic persons who either (a) have autosomal dominant family history with one or more cases of early onset AD; or (b) have a relative with confirmed early onset AD (PSEN1/2 or ABPP). DTC APOE testing is not advised. For families in which autosomal dominant AD is unlikely, genetic counseling emphasizes the limited clinical utility (Robertson and Kerruish, 2012) and poor predictive value of genetics in AD, and explores motives for pursuing genetic testing. Detailed counseling recommendations and a flow chart are provided as well as a wealth of resources for interested persons (See Figure 5) (M.R. Cassidy et al., 2008; Goldman et al., 2011).

5. Parkinson's disease

PD is the second most common neurodegenerative disorder, and as for AD and HD, intensive efforts are currently underway to identify early markers of the disease that precede the overt presence of diagnosable disease, and corresponding efforts to identify individuals with a high risk of developing disease due to genetic or environmental factors, or both. Earlier identification of parkinsonism and its related dementias may be critical to the design of experimental therapeutics to forestall dysfunction and maximize quality of life, once possible disease-modifying or neuroprotective treatments are identified (Postuma et al., 2010; Postuma and Montplaisir, 2009). Several PD genetic loci have been reported, and at least six pathogenic genes have been identified: alpha-synuclein, parkin, DJ1, PINK1, LRRK2, and ATP13A2 (See Table 1). Families with mutations in one or another of these genes demonstrate either recessive or dominant inheritance patterns, depending on the gene, and have onset of PD symptoms and signs from the second to the sixth decade. In addition, recent studies have shown an association between heterozygosity for a mutation in GBA1 (homozygous mutations in this gene cause the childhood leukodystrophy, Gaucher disease) and a common genetic contributor to PD (Sidransky and Lopez, 2012). The mechanism underlying this association remains unknown. At present, genetic counseling for GBA1 is complicated, since most patients with GBA mutations never develop PD; clarification of the sensitivity and specificity of GBA1 mutations will be needed before the utility of genetic testing for this gene is understood. As mutations in this gene are more common in the Ashkenazi population, the utility of genetic testing for this gene may depend on ethnicity, among other factors. Several reviews of PD genetics have been written, emphasizing the (limited) clinical applications, as well as the research relevance, and the potential for new genes to reveal novel therapeutic targets (Coppede, 2012; Hardy et al., 2006; McInerney-Leo et al., 2005; Pankratz and Foroud, 2007). For instance, alpha-synuclein is often considered a promising target for sporadic PD due to its deposition into Lewy Bodies. However, the rarity of cases with mutations in alpha-synuclein coupled with the uncertainty about alpha-synuclein mechanism(s) has made it a somewhat less attractive target for drug development. In contrast, LRRK2 mutations are much more frequent, occurring in 1-4% of

PD worldwide and up to 40% in some populations (Nichols et al., 2005). A familial history of PD is shown in less than 20% of cases, however, and only a minority of these follows Mendelian inheritance patterns. The majority of PD cases are sporadic, likely resulting from a combination of polygenic inheritance, environmental exposures, and complex gene-environment interactions superimposed on neuronal dysfunction due to aging.

Additional genes have been identified in hereditary disorders with phenotypes that overlap clinically with PD, such as frontotemporal dementia with parkinsonism (FTDP-17; (Hutton et al., 1998)), X-linked dystonia parkinsonism (XDP), and some of the spinocerebellar ataxias (SCA; (Subramony et al., 2002)). There have been an increasing number of susceptibility genes found with contributions to PD (Pankratz et al., 2009). Interest in predictive testing for PD is high (>60%) and surveys suggest that this number increases to over 71% when a clinical trial is available and will reach 90% of first-degree relatives for PD if a neuroprotective therapy becomes available (Dahodwala et al., 2007). Although one could apply the “HD model” for predictive testing of dominantly inherited Parkinsonian conditions (such as alpha-synuclein), the majority of the known genetic contribution to PD at this time is through recessively inherited genes or genetic variants that increase PD susceptibility or risk—like the ApoE4 variant in AD. In addition, the absence of a genetic risk factor does not insure that an individual has no risk of developing Parkinson's disease, as sporadic cases can occur. All of these issues complicate the use of even diagnostic testing, let alone predictive testing, at this time. McInerney-Leo and colleagues provide a compendium to be used to help determine the likelihood of genetic testing yielding an informative test result (See Table 7) (McInerney-Leo et al., 2005).

Parkin gene mutations are identified in 60-70% of the rare cases of PD patients with onset before age 20 and in about 27% of PD patients diagnosed by age 30, suggesting a reasonable role for genetic testing in this subgroup of patients (McInerney-Leo et al., 2005). There are some research studies using the Neuro-QOL system that have been conducted in PD. The Neuro-QOL system was developed and validated using over 3100 participants (specifically, there were 120 individuals with PD represented in the validation sample (Gershon et al., 2012). While much of the currently available published data on the Neuro-QOL does not report PD participants separately, there are published data specific to PD for Positive Affect and Well-Being item banks. For PD, this scale has a mean of 54.40 (SD 7.7); internal consistency is excellent (.94), 1-week test-retest reliability is very good (.86), and there is strong support for concurrent validity (i.e., significant correlations with the Barthel Index, Karnofsky performance Scale, Symbol search raw, PROMIS Global Physical health, PROMIS global mental health, the pain scale, Eq5D, and global HRQOL (Salsman et al., 2013)). Furthermore, there was evidence for responsiveness to change for the combined neurological sample (patients who reported changes in physical, emotional, cognitive, social/family, symptomatic well-being, and overall quality of life also reported corresponding changes in the Neuro-QOL Positive Affect and Well-Being item bank (Salsman et al., 2013).

6. Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) has been considered a member of a disease continuum including AD and PD. Clinically, patients experience memory impairment similar to AD, motor symptoms as seen in PD, and also have prominent visual misperception and hallucinations. The neuropathological hallmark is widespread presence of alpha-synuclein-positive neuronal inclusions, called Lewy bodies. Only one large genome wide linkage study for DLB has been reported to date, and although a locus was determined on chromosome 2, no simple pathogenic or gene dosage mutation was found (Bogaerts et al., 2007). Molecular genetic investigations in cohorts of patients with DLB have revealed variations in genes that

are involved in the pathogenic pathways leading to related neurodegenerative disorders such as PD (SNCA) and AD (APP, PSEN1 PSEN2). A growing literature supports the hypothesis that AD, PD, and dementia with Lewy bodies (DLB) represent differential expression of the same disease continuum. Genetic testing for DLB is only performed as part of exploratory research at this time, and no predictive testing is available.

7. Frontotemporal Dementia

Frontotemporal dementia (FTD) is the third most common cause of dementia beginning before age 65. FTD is a heterogeneous degenerative disorder encompassing a number of different clinical syndromes though the most common type presents with personality and behavioral changes and less common subtypes are described with primary language impairment (Cairns et al., 2007; Gorno-Tempini et al., 2004; Rohrer et al., 2009). There is an overlap of FTD with motor disorders such as the parkinsonian disorders, corticobasal syndromes, progressive supranuclear palsy (PSP), and motor neuron disease (Kertesz et al., 1999; Lomen-Hoerth et al., 2002). At least seven genes are currently known to cause FTD, of which three are relatively common (microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and the C9orf72 repeat expansion discussed below. There are 40 mutations described in the *MAPT* gene and over 60 mutations in the *GRN* gene; presenting manifestations, primary diagnosis, and age at onset are highly variable even within families. About 40% of persons diagnosed with FTD do have a family history that includes at least one other relative who also has or had a neurodegenerative disease. In approximately 15–40% of all FTD cases a gene mutation is identified, although most cases are sporadic. Mutations in *MAPT* and *GRN*, both on chromosome 17, each account for 2%–10% of all cases and 10%–23% of familial cases. The newly identified C9orf72 repeat expansion has been reported to account for up to 40% of familial FTD. Current genetic research shows that if a diagnosed individual has no family history of neurological disease, there is less than a 10% chance that they carry a mutation in a currently known FTD gene. Genetic testing for FTD and related disorders is complex, however, and making the decision to refer a family can be difficult. Goldman et al., (2011) present an exemplary review of studies to date with a recommended algorithm for assisting physicians with referral decisions (Goldman et al., 2011). There are very few reports of health-related outcomes following genetic testing for FTD. Survey results suggest that 50% would take a predictive test but the actual uptake rate is between 7 and 17% (McCrae et al., 2001; Riedijk et al., 2009; Steinbart et al., 2001). Quaid provides a summary of the handful of papers addressing genetic counseling and genetic testing for FTDs (Quaid, 2011). Findings suggest that 93% of tested individuals believed that testing was beneficial, although anxiety and depression were noted in both mutation carriers and noncarriers (Molinuevo et al., 2005; Steinbart et al., 2001). Goldman et al., provide case summaries to highlight some key issues encountered in genetic counseling for FTD and recommend strict adherence to HD predictive testing guidelines. Because several different genes can be involved in FTD, it is important to know which gene or genes were analyzed, and what methods were used. A negative test result does not necessarily exclude the possibility of a genetic cause for FTD, because an unidentified mutation in the gene that may have been analyzed or a mutation in a gene that may not have been analyzed. With the recent discovery of the C9orf72 mutation, some researchers feel that the majority of familial FTD can now be attributed to one of the known autosomal dominant genes (Hsiung and Sadovnick, 2007).

8. Amyotrophic Lateral Sclerosis

Over 90% of adult-onset cases of Amyotrophic Lateral Sclerosis (ALS) have no family history and are sporadic. Currently, there are five known genes found in Familial ALS (FALS). Approximately 30% are caused by mutations in the newly identified C9orf72 gene,

15-20% are caused by mutations in the SOD1 (superoxide dismutase) gene, and 7-8% of cases are caused by pathogenic variants in the TDP-43/TAR DNA binding protein 43, FUS/TLS gene or the valosin-containing protein (VCP) gene (Gitcho et al., 2008; Kwiatkowski Jr et al., 2009; Nalbandian et al., 2011).

The C9orf72 gene, whose function is still unknown, normally carries a small number of copies of a six-nucleotide sequence, denoted CCCC GG. In late 2011, two independent teams simultaneously announced that a large proportion of familial ALS cases were due to an expansion of the repeated section, that lead to hundreds or thousands of copies of the six-nucleotide sequence (Chio et al., 2011; DeJesus-Hernandez et al., 2011a; DeJesus-Hernandez et al., 2011b; Mok et al., 2012). Detailed analyses of populations throughout the world have since determined that the C9orf72 repeat expansion accounts for approximately 30% of all familial ALS in North America and 44% in Europe. It also explains about 5% of all sporadic (non-familial) cases worldwide, making it the most common known cause of ALS. Overall, the C9orf72 repeat expansion accounts for 40% of all FTD cases (Nalbandian et al., 2011; Savica et al., 2012).

Clinical testing for the C9orf72 repeat expansion is available, both as a stand-alone test and, in one commercial laboratory, as part of a “Complete ALS evaluation” 8-gene panel estimated to cover about 70% of familial ALS (Athena Diagnostics, 2012). Predictive testing for ALS and quality of life after predictive testing have not yet been reported.

9. Prion Diseases

Prion diseases are fatal neurodegenerative diseases in humans and animals caused by the misfolding and aggregation of prion protein (PrP). Although it is well established that prion diseases are under strong genetic control, few risk factors are known, aside from the PrP gene locus (PRNP) (Mead et al., 2012). About 85% of prion disease is sporadic and 15% is familial. Familial prion diseases include Creutzfeldt-Jakob disease (CJD), Gertmann-Straussler disease (GSS) and fatal familial insomnia (FFI), all of which are a result of dominant mutations in the human prion protein (PRNP). Over 30 PRNP mutations have been identified as well as coding polymorphisms that are associated with phenotype and risk variations. No known study has documented health related outcomes following predictive testing for prion diseases. However, the clinical application of sound genetic counseling is provided by Williamson & LaRusse (Williamson and LaRusse, 2004) and ethical considerations in presymptomatic testing for variant CJD is addressed in Duncan et al., (Duncan et al., 2005a). The latter paper suggests a paradigm similar to that used for HIV screening that involves compulsory testing of all blood/organ donors and individuals undergoing surgery to limit disease transmission.

10. Hereditary ataxias

The first ataxia gene (spinocerebellar ataxia type 1 (SCA1)) was identified by a research team led by Drs. Orr and Zoghbi in 1993 and, as of today, over 36 autosomal dominant cerebellar ataxias, 20 autosomal recessive, two X-linked and several forms of mitochondrial defects are known (Orr et al., 1993). Even now, in 40% of familial ataxia cases, no responsible gene abnormality is identified (Matilla-Dueñas et al., 2012; Sailer and Houlden, 2012). With the rapid advances in genetic sequencing (Wang et al., 2010) the discovery of additional genes is likely to continue. Therefore, genetic testing of at-risk asymptomatic adult relatives of patients with autosomal dominant ataxia can only be performed if the specific mutation for the family disorder has been identified. The cost of diagnostic testing for multiple, clinically-indistinguishable genetic forms of ataxia, combined with poor insurance coverage for genetic testing, presents a barrier to accurate genetic diagnosis for this group of diseases. In general, predictive testing for the dominantly inherited, adult-onset

ataxias would appropriately follow the guidelines developed for HD. Progress in the field creates a challenge for genetic testing professionals such that fairly recent guides (Nance, 2003b) are likely to miss emerging genetic advances and/or ethical concerns (Marino et al., 2011; Nance, 2003a, b).

There are publications documenting health-related QOL factors following genetic testing for ataxias. In general, no significant adverse events were documented and measures of depression, anxiety and psychological distress did not reach clinically significant levels (Cannella et al., 2001; Gonzalez et al., 2004; Paneque et al., 2007; Paneque et al., 2009). Interestingly, at-risk persons with less experience with the disease expressed greater anxiety and depression, although levels of elevated depression returned to normal limits by the 6-month assessment. Greater interest in genetic testing was associated with decreases in measures of psychological distress (Paneque et al., 2007). An opinion survey administered to at-risk family members suggested that the majority of respondents want the ability to receive genetic testing, and nearly half also want the opportunity to use prenatal testing (Nance and Ludowese, 1994).

11. Dentatorubral-pallidoluysian atrophy (DRPLA)

Dentatorubral-pallidoluysian atrophy (DRPLA) is a progressive disorder leading to ataxia, choreoathetosis, and dementia in adults, and ataxia, myoclonus, epilepsy, and progressive intellectual deterioration in children. Age of onset ranges from 1-62 years, with a mean age of onset of 30 years. Diagnosis is based on family history, clinical findings, and detection of an expansion in the length of CAG repeats in the *ATN1* gene. Treatment is symptomatic, with appropriate environmental adaptations for dementia in adults and adapted education programs for children. Transmission of the CAG repeat from parent to child results in anticipation in which affected offspring demonstrate clinical signs at an earlier age of onset compared to their affected parent. Predictive testing requires prior identification of the mutation in an affected member of the family (Pagon, et al., 1993-2013). No reports of quality of life following predictive testing are reported. DRPLA is an example of rare conditions for which predictive testing may be feasible for some at-risk family members, but for which little is known regarding the impact of the test results on quality of life. However, potential harms, particularly for those with preexisting emotional distress, and benefits from predictive genetic testing, as reported for other inherited neurodegenerative diseases, including desire for information for advance planning, monitoring developments in the field, assisting in coping with uncertain risk status, and enrolling in research studies (Roberts and Uhlmann, 2013), may be relevant for this population and other rare inherited neurodegenerative conditions.

12. Wilson's Disease

Wilson's disease (WD) is a disorder of copper metabolism that can present with hepatic, neurologic, or psychiatric disturbances, or a combination of these, in individuals ranging from age three years to over 50 years. The disease gene responsible for Wilson's disease, known as the *ATP7B* gene, is located on the long arm (q) of chromosome 13 (13q14.3) and inherited as an autosomal recessive trait. The protein regulated by this gene plays a role in the transport of copper (copper-transporting ATPase). *ATP7B* is the only gene known to be associated with Wilson's disease, and predictive molecular genetic testing of the *ATP7B* gene is clinically available. Prenatal testing for pregnancies of couples who have a child affected with Wilson's disease is possible when the disease-causing mutations have been identified in the affected family member, or if linkage has been established in the family. Molecular genetic testing is important for determining the genetic status of at-risk siblings so that therapies can be initiated before symptoms occur (Medici et al., 2007). Treatment of

individuals with Wilson disease by copper chelating agents or zinc can prevent the development of hepatic, neurologic, and psychiatric consequences in asymptomatic affected individuals, and can reduce deleterious effects in symptomatic individuals. Additional treatments, including dietary restriction of foods high in copper and antioxidant supplementation, are often prescribed. Orthotopic liver transplantation is used for individuals who fail to respond to medical therapy or cannot tolerate it. Both carrier testing and testing of as-of-yet unaffected siblings of an affected individual are recommended. However, there are no known HRQOL following genetic testing for WD (Farrer et al., 1991).

13. Direct To Consumer (DTC) testing

A number of companies offer online Direct-to-Consumer genetic tests, where consumers order test kits over the internet and send a DNA sample (usually saliva or a cheek swab) to a laboratory for analysis. The results are available to the individual over the internet after several weeks. These tests are currently poorly regulated and, thus, the quality and reliability of the results vary. Counseling may be available but is not required. The Genetics and Public Policy Center at Johns Hopkins University prepared a list of direct-to-consumer genetic testing companies as a resource for researchers, policymakers, and others who have an interest in tracking the industry. The report compiled in 2009 listed 40 separate companies offering tests for health-related conditions, whereas the report in 2010 had 30 companies and the list compiled from 2011 had 20 companies marketing direct-to-consumers and 7 companies marketing to physicians. With regards to diseases relevant to this review, nine companies market DTC genetic tests related to risk for AD, nine for MS, three for PD, three for ALS, two for PSP, one for Niemann-Pick disease, one for CJD, and one for vascular dementia. Costs range from \$300 to \$1200. Unlike the assays described in the review above, which focus on specific genetic mutations or variants in specific genes linked to a disease, most of the genetic tests being marketed to consumers are based on associations between single-nucleotide polymorphisms (SNPs) and the presence of a disease. These SNPs are generally known to have a probabilistic relationship with the disease, not a causative relationship (the difference between “20% of subjects with disease X were found to have SNP Y, as compared with 10% of the general population,” compared to “14 individuals from 3 generations in 4 of 20 unrelated families had disease-causing CAG repeat expansions in the SCA 2 gene”). Understanding and communicating the relevance of a reported genetic association to an individual is not simple, and requires a sense of the solidness of the association (Has it been replicated, and in what ethnic groups? Is this SNP within the disease gene, and is it in fact a mutation associated with the disease? What does it mean if the person carries two copies of the SNP?) It is not clear that buyers of DTC tests will appreciate the subtleties of probabilistic risk, particularly when there is no provision for professional counseling about the test and its results. Further research will be needed to determine the impact of DTC genetic testing on health care outcomes.

14. Summary of safety/benefit of predictive testing in neurodegenerative diseases

The current review revealed about 41 studies examining health related outcomes following predictive genetic testing for neurodegenerative disease. The majority of this research was for HD (28 studies or 71%) with the other studies focusing on AD, FTD, and the ataxias. In general, data suggest that predictive testing is feasible and safe for dominantly-inherited disorders. Collectively, these studies have shown that (a) extreme or catastrophic outcomes are rare; (b) consequences commonly include transiently increased anxiety and/or depression; (c) most participants report no regret; (e) many persons report important benefits from receiving the genetic information; and (f) stigmatization, discrimination, and

environmental effects are poorly understood for most genetic diseases and further policy and laws are required to protect consumers. Understanding psychosocial and quality of life outcomes following predictive genetic testing is based on data that has certain limitations. Challenges in documenting these outcomes include the potential that individuals completing the assessments may be experiencing cognitive difficulties, as well as the recognition that those who seek and complete predictive testing may not be representative of the entire at risk population for a specific disorder (Roberts and Uhlmann, 2013). Furthermore, reports of outcomes from predictive testing rely largely on studies in which individuals intentionally sought predictive testing results. Other situations (e.g., prenatal testing), may report adverse reactions with greater prevalence (Roberts, 2001).

15. Future directions for genetic counseling and consumer education

15.1 Novel protocols

With 20 years of experience showing that predictive genetic testing is safe under current protocols, it is time to consider updating and fine-tuning testing protocols. For example, flexible genetic counseling protocols are needed to address under-represented geographic regions, where there is limited in-person access to genetic counselors. Novel systems could be developed to ensure that laboratories and counselors have up-to-date information about the relationship between the presence of the gene and the presence of the disease—the current system relies on academic publication of unusual cases or aggregate data, which is a slow and potentially incomplete means of ensuring that complete information is made available in a timely fashion to practitioners. Evaluation of the impact of DTC testing on health care utilization and outcomes will help health professionals to understand how purchasers of these tests differ from patients seen in clinics, and how they handle the information they receive. Despite the impression that consequences of predictive genetic testing for neurodegenerative diseases are minor, it is important to emphasize that group data cannot alleviate the distress suffered by the few who experience significant adverse effects. Responsible health care practices must ensure appropriate care for all consumers. Novel approaches to genetic counseling might include tele-counseling, “hotlines” for genetic counseling, and public awareness campaigns to better educate and inform consumers about the complexity of genetics and health. It would be helpful for insurers to improve reimbursement rates for various creative genetic counseling practices to maximize prevention of adverse health outcomes (Hawkins, 2010).

15.2 GWAS considerations

Genome wide association studies (GWAS) examine common genetic variants and investigate their relationship to traits, including diseases. GWAS of unrelated subjects with AD have revealed, with the exception of single-nucleotide polymorphisms (SNPs) near the APOE gene region, that all SNPs described have had small effect sizes, with odd ratios from 1.1 to 1.5. A number of studies have confirmed that clusterin (CLU), phosphatidylinositol binding clathrin assembly protein (PICALM), and complement component (C3b/4b) receptor (CR1) are associated with AD (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010). Studies in familial late onset AD have replicated most of these findings (Wijsman et al., 2011). GWAS have limitations as a result of quality control, definition of clinical groups - including controls, control for multiple testing and population stratification; all resulting in a high false positive rate. As the cost of GWAS comes down, this too, may soon be offered as a DTC test to consumers or as part of an evaluation. In the future, patients might request their results of GWAS be made available to them for evaluation of risk of AD and other neurodegenerative conditions; the clinical contribution of which is unknown in AD and yet to be determined in FTD, HD, and other neurodegenerative disorders (Atkins and Panegyres, 2011).

15.3 Beyond “genetic” counseling

Genetic counseling is expanding beyond the mere explanation of simple Mendelian genetics, and will also need to expand beyond a simple assessment of immediate psychological risks and benefits of the tests. Counseling after predictive testing for a dominant disease requires new areas of expertise and content that have not yet received appropriate attention. Gene carriers have a whole new set of questions after predictive testing. The question of “whether I will get disease?” shifts to questions such as “when will I get the disease?”, “what can I do to delay disease onset?”, “how will the disease present itself in me?”, “when do I get a diagnosis?”, “when do I tell others?”, “how do I avoid being treated differently and discriminated against?”, “can I prevent or change my genetic outcome?” and “what lifestyle factors can I change or modify to delay onset of symptoms?” Once again, this refined set of questions is particularly evident in the HD testing community. Even here, where the use of predictive testing has matured over 20 years, it is not always clear which health professional should most appropriately respond to these new questions, and it is likely that the responses will change as research leads to improvements in risk factor modification and disease state identification. Others have also emphasized the importance of pastoral care to address the spiritual aspects of having genetic information about one's future (Ready et al., 2011).

15.4 Formal didactic protocols

Both clinicians and consumers are slow to move from a “black and white” understanding of genes and gene mutations to a more subtle understanding of the effects of sequence variants. Incomplete penetrance, age-dependent penetrance, and the possible clinical relevance of “intermediate” alleles, for instance, have been slow to enter into clinical discussions in the HD clinic. A detailed description of the relationship between CAG repeat size and onset age was published a decade ago, confirming a wide variation in onset ages for the most common repeat numbers. In contrast, very low repeat lengths in the mutable range and very large repeat lengths have much better predictability and might be useful to consumers in future planning and decision-making. Brinkman and colleagues published the association of onset age and CAG repeat from a large worldwide sample of over 4000 HD patients (Brinkman et al., 1997; Djousse et al., 2003; Langbehn et al., 2004). Although the study is limited by its retrospective design (i.e., reports of disease onset age were recalled and sent with a blood sample), findings offered immediate clinical relevance and a WEB site was developed for consumers and other researchers to examine. HD researchers now use a measure of current age and CAG repeat length to measure what is now referred to as “genetic burden”, “disease burden”, or simply the “CAG by age product, or “CAP score” (Henley et al., 2009; Penney et al., 1997; Zhang et al., 2012), but this concept has not yet been brought to the clinic.

15.5 Discrimination and stigmatization

Despite increasing awareness of genetic discrimination and stigmatization, no guidelines have been established to help HD families acquire information about protection from consequences. Consumer advocacy could be enhanced with more available education and opportunities for families with genetic risk to participate in policy development and information exchange. Research suggests high rates of genetic discrimination/stigmatization distress coupled with low rates of knowledge of genetic laws protecting consumers from unfair treatment (Erwin et al., 2010; J. K. Williams et al., 2010). Health care professionals might examine methods of disseminating more information about the importance of genetic information and how greater involvement is needed in policy development to parallel scientific advances.

15.6 Predictive testing in children

Predictive testing in children continues to receive a great deal of attention, with most recent debates centering on recommendations from the American College of Medical Genetics, which address reporting of incidental findings in clinical exome and genome sequencing (Green et al., 2013). These guidelines require that laboratories analyze and report mutations on specific serious and treatable conditions regardless of the indication for the test or the age of the person. The list of conditions includes those with onset typically in the adult years, and specifically excludes disorders for which sequencing is not recommended, for example, conditions caused by repeat expansions as is the case with Huntington disease (Green et al., 2013). However, the requirement that genomic sequencing information be reported on a child is a departure from the position taken by the American Academy of Pediatrics, in which one component of testing and disclosure decisions is what is determined to be in the best interest of the child (Ross, et al., 2013), and continues to generate debate regarding genetic testing on children (McGuire et al., 2013; Williams et al., 2013; Wolf et al., 2013).. The initial recommendations of all genetics organizations recommended against predictive testing of asymptomatic children for adult-onset neurodegenerative disorders (2000; Borry et al., 2006a; Borry et al., 2006b; Clarke, 1994). Unless a disease-modifying treatment can provide direct benefit to the child being tested, the ethical principles of autonomy and justice require that the individual being tested be of an age to make the decision to be tested independently, and that children within a family are treated equally. The child's rights not to be tested outweigh the parent's right to make this decision on behalf of the child for reasons of curiosity, guilt, or financial or life planning. Because of the firm initial stance of experts in the field on this topic, most of the published cases and reports in the literature describe exceptions (Duncan et al., 2005b), or differing ethical viewpoints (Malpas, 2008; Rhodes, 2006). A recent survey of 216 US genetic counselors, however, reaffirmed a support for predictive testing if it would determine disease progression or prognosis, likelihood of survival after a specific treatment, or risk for an adverse drug reaction, and a lack of support for testing for disease susceptibility in the absence of a treatment. Articulated concerns included the potential for insurance discrimination, testing in the absence of medical necessity, and loss of the child's autonomy. The availability of Direct to Consumer testing to children is of concern (Howard et al., 2011). The European Society of Human Genetics is the most recent professional group to write guidelines about the testing of children, with the advantage of almost 20 years of world experience in molecular diagnostics to build upon (Genetics, 2009). Their recommendations include the following general considerations:

1. The primary reason for a genetic test in a person who lacks capacity to consent should be that individual's direct benefit;
2. The opinion of the minor should be taken into consideration in proportion to the minor's age and degree of maturity;
3. Parents should make decisions in the best interest of the child; if the decision made by the parents is not to the direct benefit of the minor, it is the responsibility of the health care professionals to defend the interest of the minor;
4. Asymptomatic minors who are deemed to be well-informed and free of external pressures who desire a predictive test should be considered competent to undergo genetic testing;
5. Parents are responsible for informing their children of their genetic risks, with support from health professionals; and
6. Genetic counseling is required as part of a genetic testing process.

In summary, predictive genetic testing of children for generally adult-onset neurodegenerative disease is not encouraged by experts in the community, but there is a

trend to some softening in the previous firm stance on this topic, as experience with adult testing accrues and shows no major adverse outcomes, and as society increasingly recognizes that children may or perhaps should participate in their own medical decision making as they mature. It is important to comment that the restriction on predictive testing of minors should not bear on the appropriate use of gene tests for diagnostic purposes in the unusual case of a childhood onset of a generally adult-onset disease (particularly likely in HD, where juvenile onset cases represent 5-10% of all cases, and in Spinocerebellar ataxia type 2 and some of the other ataxias, where very large CAG repeat expansions have been reported with very young onset ages.)

16. Decision-making for predictive genetic testing

Feasibility of predictive genetic testing in neurodegenerative diseases for which no Mendelian genes are identified requires further consideration. It is well understood by health care professionals that the complexity of the genetic test can meaningfully alter the utility of predictive tests. Research findings to date show that decisions to test and outcomes of testing vary depending on the perceived value in the information (See Neuman et al., 2012 for an example of experimental methodology used to examine utility of predictive tests (Neumann et al., 2012)). Summaries show consensus that persons who choose to test are more educated, at greater risk for the disorder, are more predominantly female in HD, and more predominantly male for AD. Briefly addressed here are several models put forth to help determine the utility of predictive genetic testing.

Manolio (See Figure 6) adapted a figure from McCarthy that is illustrative of the risk continuum (Manolio et al., 2009; McCarthy et al., 2008). The y-axis shows the strength of the genetic effect, ranging from highly penetrant autosomal dominant genes in the high effect size end of the axis (i.e., HD) to the low genetic strength evident in rare variants with very small effect size. The x-axis depicts the frequency of the risk allele in the population. The far right end of the continuum reflects common variants that have been implicated in common diseases and the continuum extends to alleles with very rare frequency. As genes for neurodegenerative disease are described, each can be placed on this risk continuum to assist with genetic counseling.

A more thorough model involves multiple dimensions. As suggested by Bertram and Tanzi (See Figure 3,) another important continuum to consider in predictive testing utility is the complexity of the genetic test outcomes (Bertram and Tanzi, 2005). This model facilitates consideration of the continuum from a single dominant disease gene to polygenic, environmental, and all possible interactions at the other end of the spectrum. A similar model is nicely illustrated in Paulson and Igo's discerning review of the genetics of dementia where each disease is placed on a continuum from genetic to environmental influence(s) (Paulson and Igo, 2011). It is becoming increasingly evident that any simplistic model will fall short as we begin to uncover the complexities of genes, gene-gene interactions, environment, and environment-gene interactions that can impact health outcomes.

Chilibeck argues that new technologies and advanced understanding of genetic impact on health outcomes have forced reconsideration of basic questions such as "what exactly constitutes a gene" (Chilibeck et al., 2011)? As illustrated above, even with single-gene diseases new questions emerge that challenge how and under what circumstances a segment of DNA is expressed and in what ways each DNA fragment associates with other molecules and environments.

A traditional approach put forth to examine the utility of genetic testing relies on the presence of a treatment. Some experimental paradigms have used a continuum of treatment factors that might be considered for consumer decision-making about the value of predictive

genetic testing. An expansion of this idea might be helpful for future protocol development in genetic testing programs to help consumers arrive at decisions regarding predictive tests. Figure 7 lists hypothetical treatments that might be considered for neurodegenerative diseases varying by invasiveness and frequency. As further knowledge is obtained and new treatments are developed, treatment effectiveness, cost (reimbursable or not), and side effects/adverse events would be additional factors to consider in this model. There is emerging evidence that protecting and improving brain health with vitamins, physical exercise, crosswords, and Sudoku may have an impact; these beneficial considerations require integration into these models.

17. Incorporation of genetics into the early detection of HD

Currently in its twelfth year of funding by the National Institutes of Health and CHDI Foundation, the PREDICT-HD research study has enrolled more than 1200 gene-expanded but not clinically diagnosed participants, as well as a smaller sample of demographically-matched, non-gene-expanded participants ($n = 350$) that serve as a comparison group. To date, 206 participants from the PREDICT-HD study have been prospectively clinically diagnosed. In addition, a proxy measure of “estimated years to HD clinical diagnosis” (AKA genetic burden, disease burden, CAP score, probability of diagnosis within five years) was developed and validated (Langbehn et al., 2010) using DNA and current age. Findings from this and similar studies (Paulsen, 2009) have now documented that clinical markers of disease can be detected decades before diagnosis using cognitive (Paulsen, 2011), sensory (Johnson et al., 2007; Rowe et al., 2010), or subtle motor (Biglan et al., 2009) measures and that biological markers are also evident using structural (Magnotta et al., 2009; Paulsen et al., 2006) and functional (Feigin et al., 2007; J. S. Paulsen, 2009) brain imaging measures as well as wet markers from plasma (Long et al., 2012). Longitudinal study has documented clinical and biological markers of change that might be utilitarian in preventative clinical trials (Aylward et al., 2011; Paulsen and Long, 2012). Ongoing research in this area continues to examine biomarkers from plasma, DNA, RNA, and CSF. In this regard, genetic information has led a revolution of biomarker discovery work that may contribute to earlier intervention and more feasible and efficient clinical trials. Similar advancements are evident in other neurodegenerative diseases.

18. Integration of genetic information for the diagnosis of HD

Diagnostic criteria for neurodegenerative diseases must be re-conceptualized in light of genetic findings. Validity and reliability of diagnosis will remain a top priority although a gene's presence, penetrance, and heritability can significantly impact the identification and assessment of progressive decline. Efforts have been ongoing to reconsider the diagnostic criteria for MCI, AD, PD, HIV, LBD, and Vascular dementia over the past few years, incorporating evidence from imaging and biomarker studies. We believe that it is appropriate at this time to reconsider how and when to make a diagnosis of HD, incorporating evidence from large studies such as PREDICT-HD and TRACK-HD. The research definition of HD is currently based on the presence of motor signs severe enough to warrant a 99% confidence in the clinical diagnosis. In the absence of any other criteria for diagnosing HD, this definition influences clinical practice, so that the diagnosis of HD is generally made by a neurologist who identifies clear-cut and significant abnormalities on a motor exam. This conservative approach may have been appropriate before the era of genetic testing, but has long out-lived its utility. It is now well-established, through PREDICT-HD and other similar studies, that cognitive and psychiatric disturbances are detectable decades before motor manifestation (Paulsen et al., 2008; Paulsen et al., 2006; Paulsen et al., 2001). In the context of a pre-examination genetic certainty that the individual has the gene and will someday develop disease symptoms, it should be possible to make a

confident diagnosis of HD earlier in the course of the disease, based on cognitive or cognitive + motor, or behavioral + motor symptoms, even if the motor symptoms alone have not met the clinician's threshold for diagnosis. Although the avoidance of a diagnosis might be perceived as a "good thing" by some, most HD families describe a particularly difficult time when behavioral, cognitive, functional and even subtle motor changes occur without validation of disease diagnosis by the physician. Misattribution of symptoms can contribute to conflicts with friends, family, and employers and may contribute to a perception of discrimination. Finally, major changes in life and provision of much needed care are often delayed until a diagnosis is given, and appropriate adjustments in expectations at home and the workplace also depend on the diagnosis. Persons at risk for HD have reported several adverse consequences of conservative diagnosis. Examples include (a) driving despite accidents; (b) trying to maintain a job with cognitive impairments; (c) increased stress and depression caring for children and domestic responsibilities; (d) failing to ask for help; and (e) children having to take on greater responsibility to assist parent with disease. Some think that diagnosis is simply a label representing a horrible disease, but that same diagnosis can make resources available and can allow attributions for negative outcomes. Many families have shared that "finally" getting a diagnosis helped pave the way for better relations with work, school, neighbors, family, and friends. A diagnosis of HD also allowed applications for disability and healthcare assistance that were previously inaccessible.

19. Implications for other diseases

Recent experience in the Dominantly Inherited Alzheimer Network (DIAN), investigating patients with presenilin and amyloid precursor protein gene mutations, found that concentrations of A β in the CSF probably decreased 25 years before predicted onset of symptoms and A β deposition, as measured by positron-emission tomography using Pittsburgh compound B, was found 15 years before; increased concentrations of tau in the CSF and increase in brain atrophy were also discovered 15 years before symptom onset (Bateman et al., 2012). Similarly, a recent publication from the Colombian Alzheimer's Prevention initiative (API) registry of asymptomatic Colombians carrying the presenilin E280A mutation had elevated concentrations of A β in plasma and CSF in comparison to non-carriers, consistent with A β overproduction; furthermore, mutation carriers had reduced grey matter volume and altered synaptic activation on fMRI thought 20 years before the onset of symptoms (Reiman et al., 2012). These observations suggest that abnormalities in familial AD are evident decades before symptom onset and that the timing of prevention studies will be critical to their outcomes.

20. Conclusion

The past decade has witnessed an explosion of evidence suggesting that many neurodegenerative diseases can be detected years, if not decades, earlier than previously thought. Unfortunately, these scientific advances have not yet provoked any parallel translational or clinical improvements. There is an urgency to capitalize on this momentum so that earlier detection of disease can be more readily translated into improved quality of life for families at risk for, or suffering with, neurodegenerative diseases. The purpose of this special issue was to examine tensions created by efforts to detect and diagnose neurodegenerative diseases earlier and the consequences of the resulting information for individuals, their families, and society. This broad and comprehensive review of HRQOL following predictive genetic testing provides strong support that testing is feasible, safe, and most often, beneficial. This proactive special issue can, and should, provide an impetus for progress.

Acknowledgments

We thank the PREDICT-HD sites, the study participants, the National Research Roster for Huntington Disease Patients and Families, the Huntington's Disease Society of America and the Huntington Study Group. This publication was supported by the National Institutes of Health, NS040068, 5R01HG003330, NS077946, NS054893, NRG003330, National Center for Advancing Translational Sciences, and the National Institutes of Health (NIH), UL1 TR000442-06. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Highlights

- WHO, NIH, FDA, EMEA concur regarding the need for quality of life outcomes in neurological disease
- Literature suggests that predictive testing is feasible and safe: Extreme detriments are rare and many report benefits
- Genetic testing protocols require ongoing modification
- Integration of genetics into diagnoses and treatments may be essential
- Earlier diagnosis could expedite progress for neurodegenerative diseases

Figure 1. Overview of the anatomical location of and macroscopic and microscopic changes characteristic of the neurodegenerative disorders

Overview of the anatomical location of and macroscopic and microscopic changes characteristic of the neurodegenerative disorders discussed in this review. Note that the full neuropathological spectrum of these disorders is much more complex than depicted here. When there is more than one characteristic histopathological feature, these are depicted from left to right, as indicated in the labels listing microscopic changes (e.g., the 2 panels for AD depict an A β plaque [left] and neurofibrillary tangles [right]). Reprinted with permission from L Bertram and RE Tanzi, Fig 3, *The Journal of Clinical Investigation*, 115(6): 1449-1457, 2005.

Figure 2. Benefits cited after predictive genetic testing for Huntington's disease
Reprinted with permission from JK Williams, C Erwin, A Juhl, et al., Fig 1, Genetic Testing and Molecular Biomarkers, 14(5):629-636, 2010.

Figure 3. Risk spectrum predisposing to common diseases using Alzheimer's as an example
 Reprinted with permission from L Bertram and RE Tanzi, Fig 1, The Journal of Clinical Investigation, 115(6):1449-1457, 2005.

Figure 4. Utility in predictive genetic testing

Reprinted with permission from JP Evans, Cecile Skrzyni and W Burke, Fig 1, British Medical Journal, 322:1052-1056, 2001.

Figure 5. Protocols for genetic testing of Alzheimer's Disease

Reprinted with permission from JS Goldman, SE Hahn, JW Catania, et al., Fig 1, *Genetics in Medicine*, 13(6), 2011.

Figure 6. Feasibility of Identifying Genetic Variants

Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio). Most emphasis and interest lies in identifying associations with characteristics shown within diagonal dotted lines. Reprinted with permission from TA Manolio, FS Collins, NJ Cox, et al., Fig 1, *Nature*, 461-753, 2009.

Figure 7.
Models of treatment variation by invasiveness and frequency

Table 1

Overview of established neurodegenerative disease genes

Disease	Gene	Protein	Location	Inheritance	Proposed Pathogenesis
HD	HD	Huntingtin	4p16	Dominant	Poly Q-Htt oligomers develop a toxic gain of function affecting energy metabolism, excitotoxic processes and oxidative stress
AD	APP	A precursor protein	21q21	Dominant	Altered A production (A ₄₂ /A ₄₀ ratio) and aggregation
AD	PSEN1	Presenilin 1	14q24	Dominant	Altered A production (A ₄₂ /A ₄₀ ratio)
AD	PSEN2	Presenilin 2	1q31	Dominant	Altered A production (A ₄₂ /A ₄₀ ratio)
AD	APOE	Apolipoprotein E	19q13	Risk factor	Unknown (A aggregation/lipid metabolism)
PD	SNCA	- Synuclein	4q21	Dominant	Neurotoxicity by aggregation of - synuclein
PD	PRKN	Parkin	6q25	Recessive	Impaired protein degradation via proteasome
PD	DJ1	DJ-1	1p36	Recessive	Impaired oxidative stress response
PD	PINK1	PTEN induced putative kinase 1	1p36	Recessive	Mitochondrial dysfunction
PD	LRRK2	Leucine- rich repeat kinase 2; dardarin	12q12	Dominant	Unknown
PD	ATP13A2		1p36	Recessive	Regulation of intracellular manganese homeostasis
FTD	MAPT	Microtubule-associated protein tau	17q21	Dominant	Altered tau-production (4R/3R ratio), and/or altered binding to microtubules
FTD	GRN	Granulin	17q21	Dominant	Loss of function (haploinsufficiency)
ALS/FTD	C9ORF72	Hexanucleotide repeat expansion	9p21	Dominant	RNA accumulation/loss of C9 protein function
ALS	SOD1	Superoxide dismutase 1	21q22	Dominant and recessive	Protein misfolding/aggregation and/or impaired oxidative stress response
ALS	ALS2	Alsin	2q33	Recessive	Impaired neuroprotection
Prion	PRNP	Prion protein	20p13	Dominant and risk	Transformation of PrP ^c into PrP ^{sc}

Diseases are listed in the order in which they are discussed in the text. Predictive genetic testing reflects knowledge of location and number of mutations associated with a condition. In some disorders a mutation will be family specific, limiting the potential for predictive testing to biologic relatives of a person with a known mutation. Some neurodegenerative disorders are genetically heterogenous, with rare cases being inherited in an autosomal dominant fashion in which a mutation may or may not be identified within the family.

, increase; PrP^c, normal form of PrP; PrP^{sc}, disease-associated (scrapie). *Modified and reprinted with permission from L. Bertram and RE Tanzi, Table 1, The Journal of Clinical Investigation 115(6):1449-1457, 2005.*

Table 2

Number of items and associations between Neuro-QoL adult item banks and short forms

Item bank	No. items in bank	No. items in short form	Sample n	Cronbach for short form	Correlation between SF and bank (xx/yy ^a)
Anxiety	21	8	513	0.95	0.96/0.92
Depression	24	8	513	0.96	0.96/0.94
Fatigue	19	8	511	0.97	0.98/0.95
Upper extremity function: fine motor, ADL	20	8	1,094	0.93	0.88/0.83
Lower extremity function: mobility	19	8	1,043	0.93	0.95/0.89
Applied cognition: executive function	13	8	1,109	0.92	0.95/0.82
Applied Cognition: general concerns	18	8	1,109	0.94	0.97/0.91
Emotional and behavioral dyscontrol	18	8	511	0.93	0.97/0.90
Positive affect and well-being	23	9	513	0.97	0.99/0.96
Sleep disturbance	8	8	1,087	0.85	NA ^b
Ability to participate in social roles and activities	45	8	549	0.96	0.95/0.94
Satisfaction with social roles and activities	45	8	549	0.96	0.96/0.94
Stigma	24	8	511	0.93	0.96/0.93

Abbreviations: ADL = activities of daily living; NA = not applicable; QOL = quality of life; SF = short form

Reprinted with permission from D Cella, J-S Lai, CJ Nowinski, et al., Table 2, *Neurology* 78:1860-67, 2012.^a xx = before removal of SF items from bank; yy = after removal of SF items from bank^b Sleep disturbance is a small calibrated item bank of only 8 items so we did not develop a short form.

Table 3

Health related outcomes of predictive genetic testing for Huntington's disease

Author, year	Country	Sample size	Scales used	Time point of measurement(s)	Results
Almqvist et al. (2003)	Canada (Vancouver)	106	BDI, SCL-90-R, GWBS	Baseline, 7-10 d, 2, 6 m, 1, 2, 5 y	<ul style="list-style-type: none"> • Adverse events, e.g., suicide, clinical depression occurring in a part of both groups but more frequently in GC • Overall improvement in psychological distress compared to baseline in both groups • More depressive symptoms in GC than in NC 5 years after testing
Browner and Preloran (2010)					
Codori, et al. (2004)	USA (Baltimore, MD)	153	SADS, BDI	1 y	Prevalence of major depression (3-6%) not different between GC, NC and population estimates
Codori et al. (1997)	USA (Baltimore, MD)	160	BDI, BHS	3, 6, 9, 12 m	Bad test result, no children, married and closer to estimated onset. Hopelessness and depression were higher in carriers but all levels were within normal limits.
Codori and Brandt (1994)	USA (Baltimore, MD)	68	AQ	1-6 y	No differences between GC and NC in relation to effects of test results <ul style="list-style-type: none"> • Positive and negative aspects of test result • Perceived positive outcomes outweigh negative ones • Authors suggest self-selection bias in

Author, year	Country	Sample size	Scales used	Time point of measurement(s)	Results
					persons pursuing testing
Decruyenaere et al. (2003)	Belgium (Leuven)	57	BDI, SCL-90-R, STAI, MMPI, IES, HOS	Baseline, 1, 5 y	<ul style="list-style-type: none"> • No differences between groups in general distress • GC had less positive feelings and showed more avoidance than NC • Improvement in depressive symptoms and anxiety compared to baseline in both groups
Decruyenaere et al. (1999)	Belgium (Leuven)	61	STAI, BDI, MMPI	1 y	Pre-test psychological measures were the best predictors of post-test functioning irrespective of test results
Decruyenaere et al. (1996)	Belgium (Leuven)	53	STAI, BDI, MMPI, UCL	1 y	<ul style="list-style-type: none"> • Anxiety and depression levels significantly decreased 1 y after a good test result • No significant change in anxiety and depression after a bad test result
Downing et al. (2011)	USA (Iowa City, IA)	1020	Self report, PSS, BDI-II, TFC, LES count/sum	Baseline, 2y	<ul style="list-style-type: none"> • Mid group had highest stress scores • Significant interaction between age and time since HD genetic testing found • Highest stress scores in the diagnosed group
Dudokedewit et al. (1998A and 1998B)	Netherlands (Rotterdam/Leiden)	58	IES, HDAS, BHS, SCL	6 m	<ul style="list-style-type: none"> • Variables with highest predictive potential of post-test distress included previous episodes of depression, being a female, having children and pre-test intrusive thoughts

Author, year	Country	Sample size	Scales used	Time point of measurement(s)	Results
					<ul style="list-style-type: none"> • The test result did not contribute to post-test distress
Dufresne et al. (2010)	Canada (Montreal)	135	Semi-structured clinical interview	1 w	<ul style="list-style-type: none"> • No catastrophic reactions • No expressions of regrets for undergoing the predictive testing • Most frequent reason given for predictive testing was to relieve uncertainty
Erwin et al. (2010)	USA 67.8% Australia 21.5% Canada 10.7%	443	I-RESPOND survey, MOS, ATS, MBSS, SWBS, LOT, IES	6 m to 25 y (avg= 6.9 y)	<ul style="list-style-type: none"> • 46% report genetic discrimination • 22.4% reported distinct benefits from having genetic or family history risk • Most common type of discrimination experience was relational (32.9%) although discrimination was also reported for insurance (25.9%) and employment (23.6%) • Only 11.5% of HD participants were well informed of legal protections
Gargiulo et al. (2009)	France (Paris)	119	Structured interview MINI	3.7 y (.32 to 8.9) y	<ul style="list-style-type: none"> • Depression was common (58%) in GC but no different than in NC and normal population • Only predictive variable of post-test depression was pre-test depression and did not vary by test result
Lawson et al. (1996)	Canada (Vancouver)	135	SCL-90, BDI	1 y	<ul style="list-style-type: none"> • Adverse events seen

Author, year	Country	Sample size	Scales used	Time point of measurement(s)	Results
					with equivalent frequency in GC and NC • Depression (but not gene status) predicted adverse events
Lickleder, et al. (2008)	Germany (Freiburg)	121	BDI-II, BSI, SF-12, SSQ, SOC-L9, BFS	4 y after testing	<ul style="list-style-type: none"> • Comparable mental health and quality of life in GC and NC at 4 y • Diagnosed HD subgroup showed a higher level of depression • Social support was predictive of good outcomes for both GC and NC
Mariotti et al. (2010)	Italy (Milan)	92	UHDRS, SCL-90, BDI, WAI; clinical case conference	Avg=11.2 +/- 4.6	<ul style="list-style-type: none"> • BDI scores higher in gene carriers but within normal limits • No diffs between groups at followup • No depression or suicidal ideation
Ready et al. (2011)	USA (Iowa City, IA)	15	Qualitative interviews in GC and companions	3 to 8 y (avg=5.9 y)	<ul style="list-style-type: none"> • QOL viewed with importance on the present (not the post or future) • Prominent is the importance of a positive attitude • Most difficult to cope with witnessing HD in others • Greatest concern for future is employment
Robins Wahlin et al. (1997)	Sweden (Stockholm)	4	GHQ-30, BDI	2, 6, 12, 24 m	<ul style="list-style-type: none"> • Wide range of coping strategies seen • Psychiatric and psychological competency needed for genetic counseling
Tassicker et al. (2006)	Australia (Westmead)	2036		10 y	<ul style="list-style-type: none"> • No catastrophic reactions noted • Complex and challenging issues raised to

Author, year	Country	Sample size	Scales used	Time point of measurement(s)	Results
					inform other PT centers and urge updates on worldwide guidelines • Challenging counseling issues include interpretation of test results in the mutable normal (27-35) and reduced penetrance (36-39) ranges
Taylor & Myers (1997)	USA (Boston, MA)	16	Survey	6 y (range 1-9 y)	<ul style="list-style-type: none"> • NC reported decrease in unfavorable feelings and increase in favorable feelings • GC reported no change in feelings • Utilization of health care services remained the same or increased in GC • Only NC reported increased sense of control and self-esteem with decreased uncertainty • More GC sought further education than NC
Tibben et al. (1997)	Netherlands (Rotterdam/Leiden)	86	BHS, IES	Baseline, 7 d, 6 m, 3 y	Differences in avoidance and hopelessness between groups at 7 d; equivalent at 6 m and 3 y
Tibben et al. (1993)	Netherlands (Rotterdam/Leiden)	63	Attitude Questionnaire	6 m	<ul style="list-style-type: none"> • 84% rated current life situation as being good • 81% reported that test helped with child bearing decisions • Authors note concern that denial or underestimation of the test impact on individual and family
Timman et al. (2004)	Netherlands (Rotterdam/Leiden)	142	BHS, IES, GHQ	Baseline, 7d, 6 m 1.5, 3, 7-10 y	• Long-term increase in hopelessness in

Author, year	Country	Sample size	Scales used	Time point of measurement(s)	Results
					GC compared to baseline • No long-term improvement in hopelessness in NC compared to baseline • Improvement in long-term in avoidance and intrusions in both groups compared to baseline but more pronounced for NC
Wiggins et al. (1996)	Canada (Vancouver)	146	BDI, SCL-90-R, GWBS	Baseline, 7-10 d, 1, 5 y	Improvement in mental health compared to baseline in both groups 5 years after testing
Wiggins et al. (1992)	Canada (Vancouver)	135	SCL-90, BDI, GWBS	B, 7-10 d, 6 m, 1 y	Increase in distress noted in GC at 7-10 d but all equal by 1 y; All groups (GC & NC) showed lower depression and higher well-being over time
Williams et al. (2010)	USA (Iowa City, IA)	412	I-RESPOND survey	6 m to 25 y (avg=6.9 y)	Potential discrimination from genetic testing may undermine technological advances for health care.
Williams et al. (2010)	USA (Iowa City, IA)		I-RESPOND qualitative analysis	6 m to 25 y (avg=6.9 y)	Breakdown of all benefit responses by topic
Witjes-Ane et al. (2002)	Netherlands (Leiden)	134	UHDRS	1-60 m (avg=43 m)	Greater sadness/ lower self-esteem in GC; no correlation between time of testing

d, day; m, month; y, year; avg, average; GC, Gene Carriers; NC, Non mutation Carriers; BDI, Beck Depression Inventory; SCL-90-R, Symptom Checklist 90 Revised; GWBS, Global Wellbeing Scale; BHS, Beck Hopelessness Scale; AQ, Anxiety Questionnaire; STAI, State-Trait Anxiety Inventory; MMPI, Minnesota Multiphasic Personality Inventory; IES, Impact of Event Scale; HOS Hostility Scale; PSS, Perceived Stress Scale; TFC, Total Functional Capacity scale; LES, Life Event Scale; MOS, Medical Outcomes Scale; ATS, Ambiguity Tolerance Scale; MBSS, Miller Behavioral Style Scale; SWBS, Spiritual Wellbeing Scale; LOT, Life Orientation Test; IES, Impact of Events Scale; BSI, Brief Symptom Inventory; SSQ, Social Support Questionnaire; QoL, Quality of Life; UHDRS, Unified Huntington Disease Rating Scale; WAI, Wechsler Abbreviated Intelligence scale; GHQ-30, General Health Questionnaire; GWBS, Global Wellbeing Scale

Table 4**Summary of 2012 Guidelines for the Predictive Genetic Test in HD**

-
1. All interested persons should be given current relevant information and informed consent should be documented with the person and appropriately trained and experienced health care professional.
 2. The decision to test is the sole choice of the person concerned. No input from family, friends, partners, physicians, insurance companies, employers, governments, lay organizations is considered. Only persons of at least 18 years of age are to be tested. Minors are offered genetic and didactic counseling. No exceptions for adoptions although at-risk status should be relayed. All persons are allowed testing irrespective of financial situation.
 3. Available support should be encouraged through the use of a companion or local community. Phone or telehealth is allowed when remote counseling is the only available support.
 4. Testing and counseling should be provided by experts in HD who work in collaboration with lay organizations of the country. Information is only released with the explicit consent of the person although it is considered good clinical practice for the counseling team to keep primary health professionals informed.
 5. Essential information must be communicated to the person such as: (i) at this time no proven prevention, treatment that slows disease progression, or cure is available; (ii) contact details for lay organizations and support groups; (iii) DNA facts, meaning of CAG repeat and limited information about age of onset, intermediate alleles, reduced penetrance results, feedback in symptomatic persons; (iv) possible consequences for the person, partner, children, parents and other relations, socioeconomic, employment, insurance, legal, social security consequences; (v) alternative options are given.
 6. Verification of family history is important and clinical exams provide baseline of manifestation; refusal of these testing components does not justify withholding the test.
 7. Reproductive options are shared (i) prenatal diagnosis is typically for parents already aware of their genetic risk and only if plan is to discontinue pregnancy with positive test result; (ii) preimplantation genetic diagnosis.
 8. Delivery of results occur after a minimum of one month and always given in person, all post-test counseling is available immediately and should be scheduled at the time test results are given.
 9. Contact is made within the first week after delivery of the results, regardless of the test result. If no further contact is had within one month, the counselor should initiate contact. Post-test counseling occurs regardless of financial situation. Options for additional care, education and research should be offered during this interim.
-

This table provides an abbreviated summary of highlights of new predictive guidelines for 2012 as described in *MacLeod, R., Tibben, A., Frontali, M., Evers-Kiebooms, G., Jones, A., Martinez-Descales, A. and Roos, R. 2012 Recommendations for the predictive genetic test in Huntington's disease. Clinical Genetics 9999.*

Table 5

Prior/Concurrent Studies Estimating Frequency of Genetic Discrimination

Authors	Method	Reported rate of genetic discrimination				Proportion Knowledgeable	Medical condition
		Health insurance	Life insurance	Employment	Family or social stigma	Legal protections against genetic discrimination	
Lapham, et al. (1996)	Consumer	22%	25%	13%			Various genetic conditions N = 332
Wingrove, et al. (1996)	Consumer	15.4% declined coverage based on family history 33.3% classified as "pre-existing condition" after testing					Fragile × syndrome N = 39
Shaheen, et al. (2000)	Consumer	8/126 = 6%	14/126 = 11%	1/126 = 1%			Hereditary hemochromatosis, N = 124
Hall, et al. (2000)	Third party professional	11% overall 9-36% HD				42%	Various genetic conditions N = 106
Nedelcu, et al. (2004)	Health care Professionals					45.8%	Various genetic conditions N = 271
Apse, et al. (2004)	Consumer and youth	10/470 = .02%	7/470 = .01%	1/470 = .002%		4%	Colorectal cancer N = 470
Kass, et al. (2007)	Consumer	37%		30%	18%		CF, SCD, DM, HIV, diabetes, family history of breast cancer N = 541
Bombard et al, 2007	Consumer						N=55 at risk for HD
Penziner et al., 2008	Consumer						N=15 at risk for HD
Lowstuter, et al. (2008)	Health care Professionals					31%	Not reported N = 1181
Taylor, et al. (2008)	Consumer		45/951	5/951	22% family 11% social 20% health	15%	Various genetic conditions N = 951
Bombard, et al. (2009)	Consumer		63/233=27%	16/233=6.9%	36/233=15.5%		HD
Erwin et al., 2010	Consumer	TOTAL 46%		23.6	32.9	11.5	N=443 HD
Williams et al., 2010	Consumer						N=412 HD

*Qualitative data; need to read each to estimate percentages

Adapted with permission from C Erwin, JK William, AR Juhl, et al., Table 1, American Journal of Medical Genetics Part B, Neuropsychiatric Genetics, 153B:1081-1093, 2010.

Table 6

Comparison between predictive testing for HD and susceptibility for AD

	Predictive testing for HD	Susceptibility testing for AD
Risk factors	Mendelian (with some complex expression)	Complex (with some Mendelian traits)
	Rare	Common
	Lifestyle does not moderate risk	Lifestyle moderates risk
	Late onset	Late onset
Risk communication	Low complexity of information (i.e. binary)	High complexity of information (i.e. probabilistic) ⁶⁶
	Genetically exceptional	Genetically unexceptional ^{68,77}
	High need for psychosocial support before testing ^{43,44,45}	High need for accurate interpretation after testing ⁶⁵
	Low recall error	High recall error of numeric risk ⁶⁸
		Low recall error of genotype information ⁷⁸
Psychosocial impact	Patterns of family communication are diffuse ^{5,6}	Patterns of family communication are diffuse ⁷⁹
	Low uncertainty of risk status ⁸⁰	High uncertainty of risk status ⁶⁵⁻⁶⁸
	Reports of stigmatization and discrimination ³⁷⁻³⁹	No reports of stigmatization and discrimination
	Reports of suicide and depression ³³⁻³⁵	No reports of suicide
		No significant depression ⁶⁵
	Impact of disclosure decreases over time ³⁶	Impact of disclosure decreases over time ^{65,68}

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Table 7

Likelihood of genetic testing yielding an informative test result

Family history	Age on onset	Environmental exposure	Likelihood of disease originating from alteration in a single gene
3 (including proband)	At least one dx <50 yr	No	Very high
3 (including proband)	Any age	No	High
2 (including proband)	At least one dx <50 yr	No	High
2 (including proband)	Any age	No	Moderate
No	<50 yr	No	Moderate
No	<59 yr	Yes	Low
No	Average	No	Low

These data include genes identified to date and to be identified in the future.

dx, diagnosis.

Reprinted with permission from A McInerney-Leo, DW Hadley, K Gwinn-Hardy, et al., Table 2, Movement Disorders, 20(1)11-10