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Predictive Genetic Counseling for Neurodegenerative Diseases: Past, Present, and Future

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Predictive genetic counseling for neurodegenerative diseases commenced with Huntington's disease (HD). Because the psychological issues and outcomes have been best studied in HD, the HD genetic counseling and testing protocol is still accepted as the gold standard for genetic counseling for these diseases. Yet, advances in genomic technology have produced an abundance of new information about the genetics of diseases such as Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis, and Parkinson's disease. The resulting expansion of genetic tests together with the availability of direct-to-consumer testing and clinical trials for treatment of these diseases present new ethical and practical issues requiring modifications to the protocol for HD counseling and new demands on both physicians and genetic counselors. This work reviews the history of genetic counseling for neurodegenerative diseases, its current practice, and the future direction of genetic counseling for these conditions.

Predictive testing for neurodegenerative diseases began in the early 1990s and has been accompanied by much discussion and research from genetics, ethics, and neurology communities. This review will focus on how this history has resulted in the current practice of predictive genetic counseling and testing for neurodegenerative diseases and then examine how genetic counseling for predictive testing may change in the near future with the emergence of clinical treatment trials for these conditions.

HUNTINGTON'S DISEASE

HD Gene Discovery

Before the identification of the pathogenic variant that causes Huntington's disease (HD), ethicists, geneticists, and other clinicians familiar with HD studied their patient populations and speculated about the impact of a future gene discovery. Policies were debated and protocols developed by the World Federation of Neurology Research Group on Huntington's Disease in 1990 (World Federation of Neurology Research Group on Huntington's Disease 1990) and the International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea in 1994 (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea 1994). Although predictive testing using linkage markers was available for many years, the discovery of *HTT* in 1993 (Huntington's Disease Collaborative

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Research Group 1993) introduced the possibility of providing individuals who were symptomatic or who were at risk for HD with a definitive diagnosis or risk status without the involvement of relatives. Many scholarly articles and qualitative research studies were published about the impact of predictive testing on the individual, the family, and society (Almqvist et al. 1999, 2003; Decruyenaere et al. 2004; Richards and Williams 2004; Larsson et al. 2006; Tibben 2007; Gargiulo et al. 2009). Thus, HD became the gold standard for predictive testing of neurodegenerative diseases.

The HD Predictive Counseling and Testing Protocol

The HD predictive testing protocol was developed in 1994 to facilitate the opportunity for at-risk individuals to make informed decisions about predictive testing and to provide genetic counseling and testing to those who choose it in the safest way possible (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea 1994; Huntington's Disease Society of America 1994). Among the key points of the guidelines were not testing minors, using caution when testing informs about another individual who does not wish to know their status, delaying testing for those individuals with active major psychiatric conditions until their psychiatric symptoms could be stabilized, and having participants bring a support person with them to counseling and result sessions. The guidelines were very prescriptive about the pre- and posttesting appointments (Table 1): the timing of appointments in the testing protocol, the information that should be included in genetic counseling, and confidentiality. These guidelines were updated in 2013 by the European Huntington Disease Network to include the availability of genetic counseling to minors requesting testing, as well as additional recommendations for prenatal and preimplantation genetic diagnosis and research involvement. Remarkably, the

Table 1. HDSA 1994/2003 protocol versus 2016 revised protocol

1994/2003 protocol[a]	2016 revised protocol
Telephone screen	Telephone screen
Visit 1: In-person genetic counseling (with support person, strongly advised)	Visit 1: In-person (with support person, strongly advised) Genetic counseling Sign informed consent document Mental health assessment Neurological examination offered Draw blood
Visit 2: Psychiatric assessment	Visit 2: Disclosure of results in person Arrange postresult follow-up
Visit 3: Neurological evaluation offered Review of potential impact of the test Informed consent Blood draw	N/A
Visit 4: Disclosure of results in person (with support person strongly advised)	N/A
Telephone follow-up: Additional visits for supportive counseling as needed Neurological evaluation for those testing positive	Telephone follow-up: Additional visits for supportive counseling as needed Neurological evaluation for those testing positive

Data from Huntington's Disease Society of America 1994, 2016.
[a]The order of the genetic counseling, neurological evaluation, and psychological assessment may vary.

basic tenets of the original guidelines have persisted internationally (MacLeod et al. 2013).

In the United States, the Huntington's Disease Society of America (HDSA) has published its own guidelines, which were revised several times. Although original guidelines were similar to those of the World Federation of Neurology and International Huntington Association (Huntington's Disease Society of America 1994), the last revision had some significant differences. This last revision (Huntington's Disease Society of America 2016) was undertaken to address concerns about the paternalism in the approach to previous guidelines and improve access by reducing the time required for and expense associated with testing. The protocol allows for more flexibility, such as allowing the participant to test without a support person or a neurological evaluation if they so choose. However, the biggest change is the reduction in the number of required in-person appointments from four to two (see Table 1): (1) genetic counseling, mental health assessment, neurological exam, informed consent, and blood draw; and (2) return of results. This new protocol was received with both praise (Huntington's Disease Society of America 2016) for improving access to testing and criticism (Groves 2017) for lessening some safety features, including reducing the time for the participant to reflect on the genetic counseling discussion and no longer requiring the neurological examination to assess early symptoms. Presently, HD centers are assessing their own patient populations and resources and revising protocols accordingly. Perhaps the largest contribution of the latest HDSA protocol is to prompt centers to consider each request on a case-by-case basis.

Outcomes of Predictive Testing for HD

Well before the discovery of *HTT* and even before linkage testing, the potential for predictive testing for HD created concerns about discrimination, stigma, and psychological well-being (Rosenfeld 1984; Bird 1985; Craufurd and Harris 1986; Farrer et al. 1986; Kolata 1986; Bloch et al. 1987; Kessler 1987; Lamport et al. 1987; Quaid et al. 1987; Huggins et al. 1990; Tibben et al. 1990). Whereas original estimates of the rate of uptake of testing were 55%–80% of those people at risk (Barette and Marsden 1979; Tyler and Harper 1983; Kessler et al. 1987), the actual percentage of at-risk individuals choosing *HTT* testing when it became available was only 4%–24% (Tibben 2007; Morrison et al. 2011; Baig et al. 2016). Thus, those people coming for testing are a self-selected group who may feel that the benefits of learning their results outweigh the fears of the devastating results.

Many studies looking at the outcomes of predictive testing have revealed that most of those within this self-selected group ultimately cope effectively with the information regardless of their result, yet some do experience significant psychological distress (Almqvist et al. 2003; Crozier et al. 2015). Some of the studies that reveal negative outcomes include a 1999 study, which found that ~1% of those who underwent testing experienced a catastrophic event (CE) such as suicide, suicide attempt, or psychiatric hospitalization (Almqvist et al. 1999). Approximately half of these participants had begun to manifest symptoms of HD. Those at risk for CEs were more likely to have had preexisting psychiatric problems, been unemployed, and recently diagnosed with HD.

A later study of people who had gone through HD testing found that 54% of those who tested positive had some suicidal ideation (Larsson et al. 2006). Yet, overall, the distress levels of both those testing positive and those testing negative returned to baseline levels after one year. Interestingly, most people testing positive experienced distress soon after the delivery of test results, whereas the distress of people testing negative peaked six months after the return of results (Lawson et al. 1996; Tibben 2007). Psychological distress was more common in those with positive results who felt guilty about risks to their children and those experiencing early signs of HD. The distress of the people testing negative was more common when they strongly identified with HD. Whether because of test results, prior marital strife, or early disease symptoms, many partners of those being tested also experienced distress and some relationships suffered (Decruyenaere et al. 2004; Richards and Williams 2004; Tibben

2007). Unsurprisingly, a prior history of depression was more often associated with posttest depression (Gargiulo et al. 2009). Of the 10% of participants in the Prospective Huntington At-Risk Observation Study (PHAROS) who chose testing, more than half of those testing negative experienced a reduction in depressive symptoms, whereas >60% of the positive participants had the same or higher levels of depressive symptoms than before testing (Quaid et al. 2017).

Overall, it seems that the predictive testing process generally attracts a self-selected sample of at-risk people who can cope better with results: Many people drop out of the process after counseling but before they receive results reporting reasons that included feeling unprepared to live with positive results (Ibisler et al. 2017; Mandich et al. 2017). Further, Tibben suggested that many people who have chosen to test are lost to follow-up and that those people may be experiencing psychological distress that is not captured by studies. Thus, research into the long-term impact of predictive testing may not fully reflect psychological well-being of those at risk for HD who chose to undergo testing (Tibben 2007). Another caveat is that the impact of testing has been studied only at centers that follow the international guidelines. Collectively, the evidence suggests that although many people proceed with predictive testing without long-term adverse outcomes, some experience negative outcomes, and attention to the HD guidelines may reduce the potential for negative repercussions.

The Predictive Testing Genetic Counseling Session

The international guidelines express the importance of genetic counseling and provide specific instructions about the content of a pretest predictive counseling session. The session is divided between giving and gathering information and anticipatory guidance about the posttest period. As an HD counselor, I have found that although a concrete set of information should be imparted, the patient will dictate when in the session they are prepared to hear specific information (Table 2). Beginning genetic counseling by inquiring about the patient's experience with the disease allows the counselor to assess the patient's understanding of the disease as well as any misperceptions and to learn their responses to experiencing HD in their family member(s) and their fears about the future. The genetic counselor can then use this information to explore feelings about being part of an HD family and living at risk for the disease and how the patient has managed living with the threat of the condition. The counselor may emphasize that there is significant variation in how each person with HD experiences the disease course. The counselor can facilitate patient understanding that in the event that she or he tests positive for HD, her or his personal experience may differ from that of their family member because of variability of clinical symptoms, personality, support, environment, or new treatments. Genetic counseling integrates this information into discourse about the patient's experiences. Often, misperceptions are expressed. By describing the symptoms of HD (psychiatric, motor, and cognitive) and reinforcing the disease variability, the counselor can address specific misperceptions. The counselor can refer to the patient's pedigree to discuss probable age of onset of symptoms and the concept of anticipation in which age of onset gets earlier with each generation because of an

Table 2. General HD information to include in genetic counseling

Explanation of autosomal-dominant inheritance and risk to the patient, relatives, and children
Description of DNA, the CAG expansion in *HTT*, and how the expansion produces a toxic protein that causes HD
Explanation of the four repeat ranges that can be seen in a test result: ≤26 = normal, 27–35 = intermediate–normal phenotype but expandable, 36–39 = reduced penetrance and expandable, ≥40 fully penetrant
Reverse correlation between age of onset and number of repeats
Anticipation (usually through the paternal line) and the possibility of juvenile HD

expansion of the pathogenic CAG repeat in *HTT*.

Before helping the patient to anticipate possible ramifications of testing, learning about the patient's motivation for pursuing predictive testing at this point in time may illuminate the context into which the information will be received and who is available to help support the patient. Common reasons for predictive testing include making reproductive decisions, life planning, and managing uncertainty. Communicating relevant information about HD facilitates patient engagement to think through and weigh the various consequences of following through with testing or not, to make an informed decision. The counselor may ask the patient to consider their responses to the following questions:

1. What do you anticipate your immediate reaction to a positive and a negative test result may be?
2. Over the long term, talk me through how you imagine you will manage living with knowing your risk status and coping with the stress.
3. What, if anything, about your future life plans may change?
4. With whom will you share your results? Have you discussed your testing decision with these people?
5. How are these results likely to affect these people?
6. What are your resources and who makes up your primary support system?
7. If your siblings are testing, how do you anticipate feeling if their results differ from yours?

During the session, the genetic counselor also questions the patient's support person about how she or he thinks the patient will cope with results and what they anticipate their own response will be. The counselor should explore the support person's feelings, especially when they differ from those of the patient. The genetic counselor may make the recommendation to delay testing until unresolved issues between a couple are addressed and/or may refer them for longer-term counseling.

In ending the session, the counselor communicates the next steps in the pretest protocol. If not already discussed, information can be provided about reproductive options, insurance, and resources such as the HDSA. Whether the patient decides to test or not, the opportunity to participate in observational studies is offered, which provides a way for at-risk individuals to stay connected to the medical community and, through helping further scientific understanding of HD, find some purpose for knowing they have a pathogenic variant for the disease.

How Genetic Counseling for HD May Change

The future of genetic counseling for HD will be impacted by the availability of drug trials that may provide additional hope to those found to be at risk, particularly if they lead to effective treatment and prevention. Even now, access to HD counseling in the United States is limited by the number and location of counselors sufficiently familiar with the novel characteristics of HD counseling. In many areas, access is further limited by the cost of completing the full protocol. As prevention trials become available, the demand for testing will likely overwhelm the existing resources, and new protocols will have to be established.

For example, in 2015, Ionis Pharmaceutical began a drug trial in Europe and Canada for Ionis-HTTRx, an antisense oligonucleotide (ASO) designed to reduce the abnormal Huntingtin protein through blocking translation of *HTT* mRNA. The drug showed significant success in mouse models and promising results in humans. The trial, which enrolls patients with early symptoms, has begun in the United States as a Phase 1b/2a trial. This trial—and others like it in the future—will study drug safety, tolerability, and biomarkers (Wild and Tabrizi 2017).

The availability of clinical trials of therapeutics specifically creates ethical issues for genetic counselors and physicians. Each trial will have strict inclusion/exclusion criteria—for example, the Ionis–Roche trial is only open to patients who are confirmed to have a pathogenic variant in *HTT* and are displaying early symptoms. Therefore, patients must understand that to

qualify, they will need to know their genetic status and have confirmed symptoms. Given that some patients learn their genetic status without learning their neurological status, the lure of trial participation may prompt patients to seek out more information than they would have done otherwise. It is one thing to know that you are gene variant–positive and quite another to know that you have early HD, and some patients choose not to know. A possible scenario may be that patients elect to have genetic testing to participate, learn their status, and then are not given one of the limited participant slots. If the only motivation for genetic testing is study participation, there is the potential for seeing an increase in depressive symptoms and other adverse outcomes. Additionally, one family member may be accepted into the trial while another is not. It will be up to the genetic counselor to anticipate and explore such scenarios with the patients. Genetic counseling for people wanting testing for trial candidacy could potentially impact counseling for other people who are differently motivated. The genetic counselor will have to work with her professional HD group colleagues to determine equitable access. Regardless of motivation, genetic counseling will have to include an explanation of the trial and clarification about inclusion criteria. Patients will need to understand that if a trial is a double-blind randomized study, participation will not guarantee receiving the drug, and even if they do, there is no evidence to predict benefits or harms.

Complicated as they may be, clinical trials offer hope to people when there was none before. The genetic counselor can facilitate informing people about both observational research and clinical trials. Research can offer not only hope, but a way to find meaning in their genetic status and a way to stay connected to the medical community.

ALZHEIMER'S DISEASE

Predictive Counseling and Testing for Dominantly Inherited Alzheimer's Disease

As the genes for Alzheimer's disease (AD) were being mapped, concerns were raised about the legal, ethical, and social issues of predictive genetic testing. A workshop attended by scientists, geneticists, clinicians, and ethicists formulated guidelines similar to those for HD, but also pointed to some differences between AD and HD (Lennox et al. 1994). The first report of predictive testing for AD was in 1995, soon after the discovery of the amyloid precursor protein gene (*APP*) (Lannfelt et al. 1995). A protocol that included pre/posttest genetic counseling similar to that for predictive testing of HD was accepted for AD predictive testing. However, autosomal-dominant AD can be due to mutations in three different highly penetrant genes—*APP*, presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*)—making testing more complicated than that for HD. Additionally, much of AD does not follow an autosomal-dominant inheritance pattern. Ruling out dominantly inherited AD (DIAD) does not reduce the risk for late-onset sporadic AD. Furthermore, although only ~1% of AD is due to autosomal-dominant genes, a much greater proportion is multifactorial and familial (Mayeux and Schupf 1995).

The reasons for interest in predictive testing for AD and other neurodegenerative diseases are similar to those for HD: assessing reproductive options, life planning, and managing uncertainty (Tibben et al. 1997), as well as clinical trial candidacy. As with HD, predictive testing for DIAD was found to be without significant adverse psychological consequences within the parameters of a predictive testing protocol (Steinbart et al. 2001; Molinuevo et al. 2005; Cassidy et al. 2008).

AD Susceptibility Testing and Genetic Counseling

Most of AD is not inherited as an autosomal-dominant trait, but instead is multifactorial. Through genetic counseling, individuals can better understand their empiric risk based on their family history. Still many people with a family member with AD want to undergo genetic testing and, therefore, seek out genetic counseling to learn about variants in genes that increase risk. Of the multiple genes that contribute to risk for AD discovered through genome-

wide association studies (GWASs) and exome/genome sequencing (ES/GS), the apolipoprotein E gene (*APOE*) is recognized to have the greatest association with AD risk. *APOE* has three different allelic forms (ε2, ε3, and ε4) and, therefore, six different possible genotypes. Individuals heterozygous for ε4 are at two to three times higher risk for AD than those without an ε4, and homozygotes have a significantly higher lifetime risk. Estimates of the actual *APOE* ε4/ε4-associated lifetime risk vary considerably. New studies estimate risk of AD or mild cognitive impairment (MCI) as 30%–55%, which is significantly less than early studies (Qian et al. 2017). Despite this association, APOE ε4 is neither necessary nor sufficient for the development of AD. Numerous research papers have been published cautioning use of *APOE* for either diagnostic or predictive reasons. Statements against *APOE* testing cite possible misinterpretation of risk (too much risk reduction or too high a disease risk perception) and possible insurance discrimination (CMG/ASHG 1995; Mayeux and Schupf 1995; Relkin et al. 1996; Post et al. 1997; Goldman et al. 2011). In addition to its association with late onset AD, *APOE* has been reported to lower the age of onset of early-onset AD (Corder et al. 1993; Saunders et al. 1993). The *APOE*-associated risk for AD also varies with ethnicity and sex (Farrer et al. 1997). Another distinguishing factor is that it is also a risk factor for cardiovascular disease.

Despite the guidelines against *APOE* testing, substantial interest in susceptibility testing led to a series of National Institutes of Health (NIH)-funded randomized clinical studies called the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) (Roberts et al. 2003, 2004; Marteau et al. 2005; Zick et al. 2005). In these studies, individuals at risk for AD (as a result of having a parent with the disease) were randomized to receive or not receive *APOE* results. Information concerning risk was given to both groups by genetic counselors, but only one group received their *APOE* results. The major limitation to these studies was the ascertainment bias of a largely Caucasian, female, highly educated sample. Motivation to test included anxiety about risk, desire to know as much as they could about their health, and a need to take control (Gooding et al. 2006). In general, the outcome assessments found that participants experienced little psychological distress (Cassidy et al. 2008; Green et al. 2009). REVEAL found that perception of lifetime risk was reduced among individuals with ε4 negative but not positive results, and that perceived risk may not be accurate, even after counseling (Marteau et al. 2005; Linnenbringer et al. 2010). Another interesting finding from these studies was that *APOE* ε4 positive participants were significantly more likely to buy long-term care insurance. The REVEAL investigators suggested that their participants were protected by research confidentiality, whereas if the general public chose to be tested, their results would be accessible. Awareness of this testing behavior by the insurance industry could ultimately lead to higher rates for people with family histories of AD (Zick et al. 2005). One REVEAL study showed that *APOE* positive individuals were more likely to change health behaviors, including use of unproven supplements (Chao et al. 2008; Vernarelli et al. 2010). Learning that *APOE* ε4 is also a risk factor for coronary heart disease was tolerated well, possibly because participants perceived that they have more control over cardiac risk than AD risk (Christensen et al. 2016).

The main goals of genetic counseling for multifactorial AD should be to clarify individual risk by examining the empiric risk generated from family history and to explain the lack of clinical utility of *APOE* testing. Counseling should explore motivation for wanting testing and question how the patient might achieve their goal without testing. Genetic counseling can also include a discussion of some of the REVEAL study findings on health behaviors (e.g., choosing not to use supplements and to live a heart healthy life).

The New World of Alzheimer's Genetics: DTC, Clinic Trials, and Polygenic Risk Scores

Until recently, *APOE* testing for Alzheimer risk has been limited. Yet, now *APOE* testing is being offered without genetic counseling by direct-to-consumer (DTC) companies such as 23andMe

and Helix. The majority of people choosing to test seem to accept their results without much distress, and even find positive ε4 results helpful for future planning and motivation for lifestyle change. Yet, in other studies, as many as 24% of individuals experienced psychological distress on finding that they are ε4 carriers (Zallen 2018; Marshe 2019). Without pretest counseling, these individuals had not understood the meaning of the test nor considered its consequences. Additionally, testing for *APOE* on 23andMe requires users to understand that *APOE*-associated risk is dependent on ethnicity and that their overall risk is both polygenic and multifactorial. Knowledge of having an *APOE ε4* allele has been shown to negatively influence subjective and objective performance on memory tests (Lineweaver et al. 2014). Those testing positive often seek advice and guidance from their doctors who may or may not be able to help (see alzforum.org/news/community-news/genetic-wild-west-23andme-raw-data-contains-75-alzheimers-mutations). With luck, some find their way to genetic counselors. Others turn to social media support groups (such as apoe4.info) for help.

The considerable fear of AD has fostered both semilegitimate and dubious prevention claims. Alzheimer's disease prevention centers have emerged, including at academic institutions. Although such centers can help people to change lifestyles that will reduce the risk of cardiovascular disease, whether this will translate to reduced AD risk is uncertain. Moreover, these centers target a well-educated clientele that can afford extensive elective appointments and testing. Such centers are also ordering *APOE* tests as well as biomarker tests such as amyloid positron emission tomography (PET) scans, which measure the amount of amyloid on the brain. Presently, no medication can reduce this amyloid and most asymptomatic people with amyloid will not develop AD (Hellmuth et al. 2019).

To date, drug trials for AD have failed because of safety concerns or lack of efficacy. These trials were designed for people with moderate to severe disease. Since long-term observational studies show that AD biomarkers start changing 15 or so years before diagnosis, treating people in mid to late disease stages may be too late (Bateman et al. 2012). Thus, trials have now started for asymptomatic people at high risk for developing AD (Bateman et al. 2017; Lopez et al. 2019). Genetic counseling is an important component of these studies to insure fully informed consent and to reduce the likelihood of coercion, such that someone would elect to learn their genetic status only because they want to be in the trial (Grill et al. 2015). Once again, being part of research instills hope, but participants should consider how knowing their genetic status will impact their lives whether or not the experimental drug is effective. Genetic counseling can help in this process.

Polygenic risk scores are currently used in research to assess overall risk of AD, risk of conversion from MCI to AD, and age of onset of AD (Escott-Price et al. 2015; Tan et al. 2017; Tosto et al. 2017; Xiao et al. 2017; Cruchaga et al. 2018). Polygenic risk scores provide a value based on the weighted risks of multiple variants at the same time. The utility of such scores is yet to be determined, but scientists are speculating that they can even be used to determine cognition abilities in early life (Axelrud et al. 2018). These polygenic risk scores need to be validated before they can be used clinically for risk prediction. Despite this, third-party websites already exist that will generate polygenic risk scores for conditions including AD using raw data from companies like 23andMe and ancestry.com (e.g., impute .me). If the use of such scores moves into the clinic, genetic counselors will become responsible for explaining the benefits and limitations of such tests and will have to interpret results. Already physicians are ordering predictive dementia panel tests on their patients without confirming the presence of a pathogenic variant in affected family members. Often, this is performed without genetic counseling, which can lead to ill-considered actions by the ordering physician and the patient. Without an established family pathogenic variant, the presence of one or more variant of unknown significance (VUS) may result in significant anxiety for the patient.

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OTHER COMPLEX NEURODEGENERATIVE DISEASES

With the advent of next-generation sequencing, our knowledge of genetic components of disease has exploded and with it, the furthering of our understanding of disease mechanisms. In the world of neurodegenerative conditions, this proliferation of information is particularly apparent in the fields of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). These two seemingly different diseases are now perceived as being a disease spectrum. Excluding very few unique genes (particularly, *SOD1* for ALS and *MAPT*, *PGRN*, and *CHMP2B* for FTD), the two diseases overlap in causal genes. Additionally, 98% of ALS and 50% of FTD share the common pathological finding of TDP-43 neuronal and glial cytoplasmic inclusions (Turner et al. 2017). Given that up to 13.5% of ALS and 43% of FTD is familial (Crook et al. 2017), providing the most current and accurate information for families is crucial.

Unlike HD, which is monogenetic, or AD, which is either autosomal-dominant or inheritance as a single pathology, FTD/ALS can be caused by numerous genes resulting in heterogenous clinical presentations and pathologies. Of particular importance is a pathogenic hexanucleotide expansion in the *C9orf72* gene, which causes as much as 34% of familial ALS and 26% of familial FTD (van Blitterswijk et al. 2012). Clinical presentations include pure ALS, pure FTD, FTD/ALS, AD-like disease, HD-like disease, cerebellar ataxia, psychosis, and more. Age of onset and disease duration are also highly variable for this gene, as well as many of the other FTD/ALS genes. To add to the complexity, FTD/ALS genes display different disease mechanisms (e.g., dominant-negative: *MAPT*, *SOD1* vs. haploinsufficiency: *PGRN*; recessive inheritance [*SOD1* D90A variant]; and different types of variations: single-nucleotide changes, indels, repeat expansions [*C9orf72*]). Much about the penetrance of these genes remains elusive, but some appear to be highly penetrant (*MAPT, CHMP2B*), whereas others have variable penetrance depending on the variation (*SOD1*). Moreover, several case reports and research findings raise the possibility of oligogenic inheritance and discordant family results due to sporadic ALS phenocopy (Mandich et al. 2015; Giannoccaro et al. 2017). Last, *TMEM106B* and possible other risk genes have been unveiled that influence the risk of sporadic disease as well as the presentation of familial disease when in combination with various pathogenic variants (e.g., *C9orf72, PGRN*) (Nicholson and Rademakers 2016).

Previous studies have shown that, like HD and AD, predictive testing for FTD and ALS, when conducted under an HD-like protocol, results in relatively few adverse psychological or social outcomes (Fanos et al. 2011; Wagner et al. 2018). Genetic counseling includes information on multiple genes that may be causative, uncertainty about clinical presentation, penetrance, and age of onset. Presently, many ALS centers are performing *C9orf72* genetic testing on all consenting symptomatic patients, whether they have a family history or not. The rationale behind this testing is that *C9orf72* expansions have been found in a significant number of people with apparently sporadic disease (Majounie et al. 2012). Finding a genetic cause for disease can lead to better understanding of the etiology, but can also cause substantial anxiety among relatives of those with a pathogenic variant. Additionally, because many of the genes are pleiotropic, any at-risk individual should be helped to understand that if tested, they may learn whether they carry the family variant, but not how or when that gene will be expressed. Predictive testing without a known family variant involves use of a large panel of dementia and ALS genes. As a result, the possibility of multiple VUS results is significant. Moreover, 30%–40% of people with familial ALS do not have a pathogenic variant in any known ALS gene; thus, negative predictive testing will not rule out the possibility of carrying a yet-to-be identified gene (Benatar et al. 2016).

Like HD, new clinical drug studies for ALS and some other neurodegenerative diseases have commenced. Qualifying for such trials is complicated by the multifactorial etiology of these diseases. Some trials are specific to a particular genetic etiology. For example, in some situa-

tions, people will not qualify for a trial if they have sporadic disease or a genetic form of the disease other than that targeted by the trial (e.g., FTD caused by an *MAPT* variant vs. FTD-*C9orf72*). Thus, candidates undergo genetic screening but may not qualify for participation in a trial because they carry a variant in the "wrong" gene. Patients will, therefore, learn their genetic status but have no clinical recourse. Substantial pre- and posttest genetic counseling will be needed to prepare patients for these potential outcomes. Patients will need to consider how knowledge of their status will affect themselves and their relatives.

As neurologists increase the number of tests they order, clinically or within studies, the importance of genetic counseling expands. Although genetic research leads to increased understanding of disease mechanisms, it also leads to recognition of the greater complexity of the genetics of neurogenetic diseases. Genetic counseling can help patients to have realistic expectations about possible results and better understand the concepts of variable expression, pleiotropy, penetrance, genetic heterogeneity, and VUSs. Genetic counselors will continue to play a key role in informed consent and exploration of tolerance for the uncertainty that can be generated by test results. Genetic counselors will also be instrumental in ordering appropriate genomic tests.

MOVEMENT DISORDERS

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD. Although 5%–10% of PD is monogenic, the majority of these cases are early-onset, recessive forms (Lill 2016). Thus, only 2%–3% of idiopathic PD can be attributed to monogenic etiology (Domingo and Klein 2018). The α-synuclein gene (*SNCA*) causes a rare, severe type of autosomal-dominant PD. Only four point-pathogenic variants are known, and most pathogenic variants associated with *SNCA* are duplications and triplications. The duplications have low penetrance and result in a generally milder disease. Duplications have also been found in patients with sporadic disease (Ahn et al. 2008).

The most common cause of autosomal-dominant PD is a pathogenic variant in the *LRRK2* gene. Again, *LRRK2* has been identified in patients with apparently sporadic disease. However, some *LRRK2* pathogenic variants have low penetrance so these cases may not in reality be sporadic. The G2019S variant with a penetrance of <30% is especially common in North Africans (with a frequency of 39% of sporadic and 36% of familial PD) and Ashkenazi Jews (with a frequency of 28% in familial and 10% in sporadic PD) (Schneider and Alcalay 2017). Although the phenotype overlaps with idiopathic PD, LRRK2-PD tends to be tremor-predominant (as opposed to having more posture instability) and have a lower rate of associated dementia.

Genetic counseling for PD is complicated not only by issues of penetrance, but also by the presence of variants that increase disease susceptibility. The gene most important in predicting risk for PD is *GBA*. Whereas homozygous *GBA* causes Gaucher disease, heterozygous carriers are at risk for PD. This risk is both age- and pathogenic variant–dependent. *GBA* variants are particularly common among the Ashkenazi Jewish population, in which ∼15% of people with PD have a *GBA* variant, whereas only ∼3% of non-Ashkenazi Jews with PD carry one. The most common pathogenic variant for Ashkenazi Jews is N370S, which has a lifetime penetrance of <10% (Alcalay et al. 2014). Other variants may have a higher penetrance. *GBA*-associated PD resembles idiopathic PD, but may have earlier onset and faster progression and has a higher risk of psychiatric symptoms and dementia. In fact, *GBA* variants are associated with risk of Lewy body dementia.

Until recently, because of the lack of clinical use of knowing genetic information on idiopathic PD, genetic testing was rarely performed. However, with the increase in prognostic information and both observational studies on and clinical trials for genetic forms of the disease, many physicians are encouraging testing and patients are asking for it (Brüggemann and Klein 2019). Additionally, DTC testing is available. As with AD, 23andMe is offering risk assessment for PD, and as with *APOE*, testing for

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PD through 23andMe requires reading the small print. 23andMe tests only for the common Ashkenazi Jewish variants in *LRRK2* and *GBA*. If the user is not Ashkenazi Jewish, the results do little in predicting their risk for developing PD. Genetic counseling can help explain results.

Several observational studies and treatment trials for PD require knowing gene status. Most require genetic counseling for informed consent. Patients often are motivated to help PD research. However, some asymptomatic individuals participate primarily to receive their test results. Interestingly, because both *LRRK2* and *GBA* gene variants are relatively common in this population, testing an unaffected person occasionally revealed a variant in the unaffected parent. Additionally, people interested in learning their genetic status should consider their privacy and possible discrimination (Suter 2019). These issues again point to the importance of pretest genetic counseling.

SUMMARY AND THE FUTURE OF GENETIC COUNSELING FOR NEURODEGENERATIVE DISEASE

Genetic counseling for neurodegenerative diseases is evolving. Counseling for the small number of people at risk for autosomal-dominant diseases will likely remain similar to current practices. Additionally, genetic counseling will play an essential role in future clinical trials for this population. Through genetic counseling, potential participants can consider and weigh issues such as whether or not they want to learn their genetic status, whether family dynamics are causing any coercion with regards to trial participation, whether trial participation will increase or decrease stress, and whether to delay having children to participate in a trial. As clinical trials increase, new methods such as telegenetic counseling may shorten or replace in-person counseling sessions.

As soon as any treatment for a neurogenetic disease is proven effective, however, genetic counseling will change. Pretest counseling for autosomal-dominant diseases will need to refocus on the possibility that genetic testing may still leave uncertainty because of VUSs, phenotypic variability, and genetic heterogeneity. Individuals coming for testing may learn that they are positive for a gene for which the new therapeutic is not effective. And regardless of what genomic variant they carry, they will still need to consider reproductive options, impact on family dynamics, and communication of results to other family members. Genetic counseling will still be a key to informed decision-making. With any new treatment, the number of people wishing to be genetically tested will increase dramatically and outrun the number of neurogenetic counselors. At that point, testing for these autosomal-dominant diseases is likely to be performed routinely through physicians. Yet, genetic counseling will still be important for the reasons mentioned above. Thus, another important role for neurogenetic counseling will include novel delivery modes such as telegenetic counseling, advising clinicians who are ordering tests, and advising on ethical issues generated by the new interventions, including efficacy.

Most neurodegenerative disease is multifactorial, not autosomal-dominant. For these cases, risk profiles can be generated. Although changes in lifestyle may reduce risk somewhat, the underlying genetic propensity may be too great to prevent disease. Trials are studying how the combination of genetic profiling and biomarker studies can determine who and when to treat. Genetic counseling will continue to play an active role in preparing participants for such studies and helping them to interpret results. Because of the great volume of people at risk for diseases such as late-onset AD or PD, in-person counseling with current practice models will be largely impractical. New strategies, whereby delivery of information is provided online, or in other mass dissemination ways, with genetic counseling focused on helping people adapt, need to be identified. Genetic counselors can play an essential part in designing and overseeing these tools. In summary, genetic counseling for neurodegenerative diseases will continue to be essential for people at risk to understand their risk, think about the impact of knowing their risk, and determining how to adapt to that risk.

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