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Ethical Issues in Neurogenetics

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Abstract

Many neurogenetic conditions are inherited and therefore diagnosis of a patient will have implications for their relatives and can raise ethical issues. Predictive genetic testing offers asymptomatic relatives the opportunity to determine their risk status for a neurogenetic condition, and professional guidelines emphasize patients' autonomy and informed, voluntary decision-making. Beneficence and non-maleficence both need to be considered when making decisions about disclosure and nondisclosure of genetic information and test results. There can be disclosure concerns and issues of determining whose autonomy to prioritize when a patient makes a genetic testing decision that can reveal the genetic status of a relative (e.g. testing an adult child when the at-risk parent has not been tested). Ethical issues are prominent when genetic testing for neurogenetic conditions is requested prenatally, on minors, adoptees, adult children at 25% risk, and for individuals with psychiatric issues or cognitive impairment. Neurogenetic conditions can result in cognitive decline which can affect decisional capacity and lead to ethical challenges with decision-making, informed consent and determining the patient's ability to comprehend test results. The ethical implications of genetic testing and emerging issues, including direct-to-consumer genetic testing, disclosure of secondary findings from genomic sequencing, and use of *APOE* testing in clinical and research settings, are also discussed. Resources for information about genetic testing practice guidelines, insurance laws and directories of genetics clinics are included.

Keywords

ethical issues; neurogenetic conditions; genetic testing; predictive testing; testing children; incidental findings; secondary findings; direct-to-consumer (DTC); cognitive impairment; decisional capacity; autonomy

Introduction

Ethical issues arise with neurogenetic conditions just like they do in all areas of medicine. A significant difference is that many neurogenetic conditions are inherited, and therefore a diagnosis has implications for healthcare and decision-making that extends beyond the

patient to their relatives, particularly first-degree blood relatives (i.e., siblings and children). As a result, there can be ethical dilemmas with both communication and non-communication about neurogenetic conditions in families. Information may not be communicated in a timely manner or at all, and relatives may be informed who actually prefer not to know information about risk status or test results. Particularly for autosomal dominant neurogenetic conditions (e.g., Huntington disease), there are ethical considerations when testing a patient could reveal the risk status of relatives who may not want their status determined – for example, when an adult child at 25% risk requests testing, but the at-risk parent has not been tested.

Different applications of genetic testing for neurogenetic conditions (e.g. predictive and prenatal) and the patient's age (e.g. minor) can raise ethical issues (Fuentes and Martin-Arribas, 2007; Hedera, 2001; Hoge and Appelbaum, 2012; Roberts and Uhlmann, 2013; Schneider et al., 2011; Uhlmann, 2006). In addition, neurogenetic conditions can result in a decline in cognitive functioning, which can limit a patient's capacity to provide informed consent and complicate their ability to comprehend test results. Given rapid advances occurring with genetic testing, there are ethical issues that arise in both the laboratory and with clinicians in regards to results to report to the patient. This chapter will focus on the ethical issues associated with genetic testing for neurogenetic conditions, primarily with predictive genetic testing. It will also address decision-making when there is cognitive decline and will describe emerging issues resulting from the use of new genetic tests.

Core Ethical Principles and Concepts

Medical ethics can be viewed through a "four principles" framework consisting of *beneficence, non-maleficence, autonomy, and justice* (Beauchamp, 2007). Table 1 defines these terms and provides examples using genetic testing for neurogenetic conditions. The benefits and harms involved in *beneficence* and *non-maleficence* can be defined in different ways (e.g., physical health, emotional well-being, financial costs, etc.) and from different stakeholder perspectives (e.g., patients, family members, community, society). *Autonomy* is also a multidimensional concept, and there are many ways in which a healthcare provider might take action to promote patient autonomy. For example, s/he should provide sufficient education to inform patient choices about genetic testing and ensure the decision to seek testing is voluntary and free from coercion (e.g., undue influence from family members). Autonomy is also upheld by efforts to maintain the privacy of sensitive genetic information. For example, the Privacy Rule within the federal Health Insurance Portability and Accountability Act (HIPAA), which regulates the use and disclosure of protected patient health information, can be viewed as a legal means of enhancing patient autonomy. Efforts by healthcare providers and researchers to ensure confidentiality of genetic test results would also be applicable.

Justice in this context refers to the equitable distribution of the benefits and burdens associated with genetic testing. One challenge for the field has been in ensuring equal access to genetic services and genetic testing. There are relatively few clinical genetics and neurogenetics specialists, and they are generally located in major cities and not well dispersed across geographic regions (American Board of Medical Genetics and Genomics Number of Certified Specialists in Genetics). Concerns about justice also arise when

expensive new technologies are introduced into practice. For example, use of cutting-edge technologies like genomic sequencing might be critiqued from a justice perspective because of limited availability to patients with lower socioeconomic status who either a) cannot afford testing if not covered by their health insurance or b) may not even have insurance. This example demonstrates how the promotion of patient autonomy can sometimes conflict with broader notions of social justice.

Decisional Capacity

Key position statements on the ethics of genetic testing recognize the need for standards in assessing a person's capacity to consent (American Society of Human Genetics, 1996; van der Vorm et al., 2009). Decisional capacity is typically defined along a continuum and as a reflection of four decision-making abilities: *understanding, appreciation, reasoning*, and *choice*. Considerable legal and ethical scholarship has defined these abilities and the standards used to measure them (Grisso and Appelbaum, 1998). In brief, *understanding* is the ability to comprehend the meaning of information, such as the relevant facts about a genetic test. *Appreciation* is the ability to recognize how information (e.g., risks and benefits of testing) applies to oneself. *Reasoning* is the ability to compare options and infer the consequences of choices in a logically consistent manner, while c*hoice* is the ability to state a decision.

A patient's decisional capacity can be impacted by both neurologic and psychiatric conditions. For example, patients with dementia experience cognitive decline that can affect multiple abilities involved in decision-making capacity (discussed in section "Testing Patients with Cognitive Impairment"). Patients in the midst of a manic episode might exhibit impaired reasoning, making impulsive decisions that are later regretted. Meanwhile, the lack of initiative associated with depression could result in apathetic resignation to a particular genetic testing decision, as opposed to active engagement in the choice process. Even in healthy, cognitively normal populations, patient understanding can vary greatly by factors including educational background, health literacy level, and cultural or language concordance/discordance with the provider. Ways to assess decisional capacity and facilitate communication and understanding of information are discussed in the section "Testing Patients with Cognitive Impairment."

Informed Consent

Obtaining truly informed consent can be a challenge because--depending on the condition and rapid testing advances--the risks, benefits, and limitations of genetic testing may not be completely known, or they may be impossible to quantify. Furthermore, each patient weighs these aspects of testing differently depending on individual, family, religious/spiritual and cultural contexts. As noted above, there are several factors that can affect a patient's decisional capacity which can impact their ability to provide informed consent. It is important that patients understand both potential medical and psychosocial (including insurance) outcomes from a decision to test or not test. Genetic counseling can be beneficial to patients in helping them understand these genetic testing issues, facilitating decision-making and informed consent (Uhlmann et. al., 2009) [See section "Consulting with Genetics Specialists"].

Predictive Genetic Testing

Guidelines

Predictive genetic testing guidelines for Huntington disease were first issued in 1989 when testing became available using linkage analysis (Went, 1990; World Federation of Neurology Research Group on Huntington's Chorea, 1989); these guidelines were revised in 1994 after direct testing became available (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea, 1994a, b) and updated in 2013 (MacLeod et al., 2013). Predictive testing for Huntington disease (HD) paved the way for predictive testing for other hereditary neurological conditions including early-onset Alzheimer's disease (Goldman et al., 2011; Goldman, 2012; Hedera 2001), spinocerebellar ataxias (Cannella et al., 2001; Goizet et al., 2002; Mariotti et al., 2010; Rolim et al., 2006; Sequeiros et al., 2010), frontotemporal dementias (Goldman, 2012; Quaid, 2011), and amyotrophic lateral sclerosis (ALS) (Chio et al., 2014; EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis, 2012). The application of these guidelines has also been extended to hereditary cancers (Moyer and U.S. Preventive Services Task Force, 2014), cardiovascular (Sturm and Hershberger, 2013) and ophthalmologic conditions (Stone et al., 2012).

Key components of predictive genetic testing include pre and post-test counseling, informed consent, respect for the patient's autonomy, ensuring the patient makes an informed voluntary decision and in-person disclosure of results. For many patients, the decision is not to test, which is why pre-test counseling and informed decision-making are critical. Initially it was thought that the demand for testing would be high, but studies on the uptake of predictive genetic testing for Huntington disease (Bernhardt et al., 2009; Creighton et al., 2003; Morrison et al., 2011; Panas et al., 2011; Tassicker et al., 2009) and other hereditary neurogenetic conditions (Cruz-Marino et al., 2013; Cruz-Marino et al., 2015; Riedijk et al., 2009) found that the majority of at-risk individuals decide not to learn their carrier status.

The predictive genetic testing guidelines for Huntington disease also address ethical issues, including testing minors and prenatal testing, discussed below. Table 2 provides some of the recommendations that address ethical issues and that are also broadly applicable when considering predictive genetic testing for other adult-onset autosomal dominant neurogenetic conditions.

Generally, the predictive genetic tests currently offered are for highly penetrant autosomal dominant conditions. In contrast, late-onset Alzheimer's disease is a complex inherited condition where genetic risk factors such as apolipoprotein E (*APOE)* have been identified but where predictive testing offers less definitive information about the likelihood of developing AD (Tanzi, 2012). The *APOE* ε4 allele is a well-established risk factor for AD, with some studies suggesting that individuals carrying two copies of the allele have a greater than 50% lifetime risk of AD (Yu et al., 2014). However, the ε4 allele is neither necessary nor sufficient to cause AD. Given limitations in both the predictive value of *APOE* testing and treatment options for the disease, several professional organizations have issued statements that predictive genetic testing for late-onset Alzheimer's disease should not yet be offered clinically (American College of Medical Genetics/American Society of Human

Genetics Working Group on ApoE and Alzheimer's Disease, 1995; Goldman et al., 2011; National Institute on Aging/Alzheimer's Association Working Group and Relkin NR, 1996).

Predictive Genetic Testing Considerations

When a patient presents for predictive genetic testing, key questions to consider are "why now?" and "how will knowing or not knowing the results impact their healthcare and life decisions?" General ethical considerations include respect for autonomy and beneficence - assuring that the patient fully understands the testing decision and the implications of results, is freely making the testing decision (not being pressured/coerced by others) and that the benefits outweigh the potential harms. Testing should be performed during a stable time and not during a time of stressful life events (Huntington's Disease Society of America, 2016). The very nature of predictive genetic testing means that generally these decisions do not need to be made urgently and patients can take the time to think over their decision. It is important to make sure that patients are secure in their decision, not vacillating "back and forth" and will be able to psychologically handle receiving the test results. Referral to genetic counseling services can be helpful in achieving these goals (see section "Consulting with Genetics Specialists").

Care especially must be taken when predictive testing could potentially reveal the risk status of another individual who has not requested the test. This could occur with testing of an identical twin or testing an adult child at 25% risk when the at-risk parent does not want to know his or her status (as discussed below). It is important to discuss with the patient the potential for harm to the other family member who has not requested the test, as well as plans to share or keep private the patient's own test results.

Testing Minor Children

Patients diagnosed with a neurogenetic condition may subsequently wish to ascertain the status of their child/children. Testing at-risk children can be desired for a number of reasons including potential medical care, future planning, allocation of financial resources, and primarily, relief from anxiety of not knowing risk status (Duncan and Delatycki, 2006; Ross et al., 2013). Parents may feel it is their right to know this information and as guardians are responsible for decisions about medical care of their children. However, there is a distinct difference between parents deciding about predictive testing for a condition with childhood onset versus adult-onset. In making decisions about genetic testing of minors, a key consideration is whether the neurogenetic condition affects only adults or could arise in children. If there are concerns about childhood onset, the child should be evaluated by a pediatric neurologist/physician familiar with the juvenile form and tested only if clinically indicated. If the neurogenetic condition is adult-onset and there are no medical benefits to making a diagnosis during childhood, testing should be deferred until the child is 18 to preserve autonomy around this important but not urgent medical decision (Ross et al., 2013).

The National Society of Genetic Counselors (2012) issued a position statement encouraging deferring predictive genetic testing of minors for adult-onset conditions: "Deferring predictive genetic testing allows individuals to choose for themselves as adults, taking into account their own circumstances, preferences and beliefs (National Society of Genetic

Counselors, 2012).” The American College of Medical Genetics and Genomics (ACMG) jointly with the American Academy of Pediatrics (AAP) issued a policy statement in 2013 which reaffirmed their continued support to defer genetic testing of children for adult-onset conditions until adulthood (Ross et al., 2013; American Academy of Pediatrics, Committee on Bioethics, Committee on Genetics and American College of Medical Genetics and Genomics Social, Ethical and Legal Issues Committee, 2013).

Similarly, the American Society of Human Genetics (ASHG) issued a position statement in 2015, reaffirming their 1995 statement with ACMG (American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors, 1995) about deferral of predictive or pre-dispositional testing for adult-onset conditions until adulthood. The ASHG statement notes that “Providers can acknowledge that, in some cases, testing might be a reasonable decision, but decisions should follow thorough deliberation,” (Botkin et al., 2015, p. 8) including providing adolescents with the opportunity to discuss these testing issues without their parents present. While both the ACMG and ASHG statements note that predictive genetic testing for adult-onset conditions may be considered in childhood, if in the child’s best interest, to alleviate substantial distress or facilitate life-planning decisions, “a referral to genetic counselors and mental-health professionals is appropriate if the clinician and family need additional support for decision-making or in assessing the psychosocial dynamics” (Botkin et al., 2015, p. 8).

Testing an Adult Child When At-Risk Parent Has Not Been Tested

The ethical principle of non-maleficence is an important consideration when an adult child requests predictive genetic testing and the at-risk parent has not been tested. There is potential for harm to the at-risk parent--who is not involved in the decision-making and has not consented to the test--to have his or her carrier status determined when this may be information s/he does not want known. In some cases, adult children are simply not aware that their testing could reveal their parent’s status, and they subsequently will follow-up with their parent first about testing. In other cases, the adult child does not want to discuss testing with their parent (who may even have early symptoms), the parent is unavailable/deceased, or the adult child already knows that the at-risk parent does not want his or her status determined (Benjamin and Lashwood, 2000; Lindblad, 2001; Maat-Kievit et al., 1999). A key ethical consideration is also autonomy and determining whose rights take precedence – the adult child’s right to know versus the at-risk parent’s right not to know; these and other ethical issues and testing options are discussed in the above cited articles.

When there is a request to test an adult child at 25% risk, the HD predictive testing guidelines (MacLeod et al. 2013) recommend that extreme care be taken and efforts made to resolve the conflict (Table 2). Of note, although not included in the 2013 guidelines (MacLeod et al. 2013), the 1994 guidelines specifically stated “A considerable majority of representatives for the lay organizations feel that if no consensus can be reached, the right of the adult child to know should have priority over the right of the parent not to know” (International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington’s Chorea, 1994a, p. 1534).

Testing Patient's At-Risk Relatives Who Have Just Learned They Are At-Risk

When a patient is diagnosed with a neurogenetic condition, family members may subsequently request predictive testing. Particularly when there is a new diagnosis and no family history of the condition, there can be heightened anxiety and desire to learn information as soon as possible. The ethical principle of non-maleficence applies in this situation. It is important to ensure that the family member makes an informed decision about predictive genetic testing and will be able to handle the results and that the decision is not just based on anxiety and reaction to a family member's diagnosis. Referral of family members for genetic counseling can be effective in educating them about the neurogenetic condition and addressing these predictive testing decisions.

Testing Patients with Psychiatric Issues

Patients may have depression and/or anxiety from being in a family with a neurogenetic condition, living at-risk, or simply because these psychiatric conditions are common in the general population. Patients may have serious psychiatric conditions like bipolar disorder and even past suicide attempts. Of note, approximately one-third of individuals with Huntington disease will present with psychiatric symptoms and there is an increased risk for suicide (Warby et al., 2014).

The ethical principle of non-maleficence is a strong consideration when testing patients with psychiatric issues. It is important to determine whether the patient will be able to cope psychologically with a positive test result. Depending on the patient's psychological status and whether support is in place, proceeding with or potentially deferring testing should be carefully considered. In addition, a minority of patients without prior psychiatric issues will experience an adverse psychological event after or within months of results disclosure (Almqvist et al., 2003). The Huntington disease predictive genetic testing guidelines specifically recommend evaluation by a mental health professional and having a therapist identified can help facilitate follow-up for the patient after test results are disclosed (MacLeod et al., 2013).

Testing Patients with Cognitive Impairment

Testing and disclosing genetic risk information to cognitively impaired individuals raises both practical and ethical issues. The need for assessment of ability to provide informed consent is particularly important in the care of individuals with cognitive impairment, where deficits in memory and executive functioning (among other cognitive domains) may undermine decisional abilities.

Patients interested in or needing genetic testing may already be evidencing cognitive difficulties (e.g., in processing and recalling information) that compromise their ability to fully comprehend the test decision. Informed consent procedures should address these difficulties where possible; accommodations might include simplifying/reducing amount and types of information provided, using visual aids (e.g., pictographs) to help convey probabilities, and engaging a trusted partner to assist the patient in decision making (Lautenbach et al., 2013; Trevena et al., 2013). It may also be helpful to adapt validated

instruments (e.g., MacArthur Capacity Assessment Tool) for use in this context to determine whether decisional abilities are sufficiently impaired such that a surrogate should be involved in medical decision-making (Appelbaum and Grisso, 2001). Such assessments may also be necessary to inform legal judgments of competency to make medical decisions.

When the patient is clearly decisionally impaired but maintains legal authority to make medical decisions, this may place the care provider in potential conflict between legal and ethical duties to the patient. Proactive efforts to transfer power of attorney to a trusted loved one, and to have the patient complete advance directives and grant permission for release of records, may help avoid situations where legal obligations (e.g., as stipulated by HIPAA) could restrict providers from communicating information and having the patient's spouse/partner/children involved in medical decisions if not specifically legally designated. In situations where proxy decision making is required, health professionals should try where possible to confirm that the surrogate decision maker acts in accordance with patients' previously expressed wishes and obtain assent where appropriate from the patient him- or herself (see Beattie, 2007, for a review).

Prenatal Testing for Neurogenetic Conditions

Depending on the neurogenetic condition, prenatal testing may be available using preimplantation genetic diagnosis, chorionic villus sampling and amniocentesis. Advances will likely be made, with non-invasive prenatal testing expanding to include Mendelian-inherited conditions. There are significant ethical issues raised when parents request prenatal testing for adult-onset neurogenetic conditions (Hercher et al., 2016). The Huntington disease predictive genetic testing guidelines make clear that prenatal testing should not be performed if it will not impact pregnancy management; otherwise continuing a pregnancy after testing is akin to testing a minor (see Table 2 for recommendations; MacLeod et al., 2013).

The National Society of Genetic Counselors issued a position statement in 2014 stating that prenatal testing for adult-onset conditions should be deferred if pregnancy management will not be affected (National Society of Genetic Counselors, 2014; Hercher et al., 2016). A key issue is that "prenatal testing for adult-onset conditions denies the future child the opportunity to make this decision for him/herself as an adult" (National Society of Genetic Counselors, 2014). It is strongly recommended that prospective parents meet with a genetic counselor/healthcare specialist with genetic counseling expertise when considering prenatal testing for adult-onset conditions (National Society of Genetic Counselors, 2014; Hercher et al., 2016).

The American College of Obstetricians and Gynecologists (ACOG) reaffirmed their 2008 statement on Ethical Issues in Genetic Testing in 2014 (American College of Obstetricians and Gynecologists 2008) indicating that the same cautions with testing children for adult-onset conditions would apply to testing a pregnancy. ACOG's statement noted the "wrenching decisions" where "consideration also should be given to personal preference, that is, the interests individuals may have in terminating a pregnancy… that they feel

morally obliged or prefer not to bring into the world" (American College of Obstetricians and Gynecologists 2008, p. 1498).

There are significant ethical issues that arise with performing exclusion preimplantation or prenatal diagnosis for autosomal dominant neurogenetic conditions. Exclusion testing requires samples from the at-risk patient, one of the parents, the patient's partner and the pregnancy [see HDBuzz http://en.hdbuzz.net/036 for a patient-friendly explanation with diagrams]. With exclusion genetic testing, a patient's desire not to know their own carrier status is protected by only disclosing whether the chromosome of interest came from the side of the family with the neurogenetic condition ("high risk" with 50% risk) and there is no disclosure about whether or not the specific gene mutation is present. A patient who is informed that the result is "high risk" and decides to terminate the pregnancy will be terminating a normal pregnancy half of the time. In applying this approach with non-disclosing preimplantation genetic diagnosis, physicians could be forced to offer more IVF/PGD cycles, perform sham transfers and offer unnecessary prenatal testing when the conceptions may have no increased risk for the neurogenetic condition (Erez et al., 2010; MacLeod et al., 2013).

Communication/Non-Communication of Genetic Test Results

When a Patient Declines Results Disclosure

Patients may initiate predictive genetic testing for a neurogenetic condition and subsequently decide not to have results disclosed or decide to delay disclosure because the time is not right to hear their results. Ethical issues can arise when the patient decides not to have results disclosed, particularly if there is "good news." There can be a desire to inform the patient of "good news" so that s/he is relieved from living their life at-risk. Even if the predictive test results are positive, there is currently not a duty to inform/warn if the patient subsequently requests non-disclosure, cancels the disclosure appointment or does not return to clinic (see "Is There a Duty to Warn" section). The Huntington disease predictive testing guidelines make clear that results should be disclosed in person and that the patient's decision about non-disclosure should be respected (see Table 2; MacLeod et al., 2013).

If the patient decides not to learn test results, the laboratory fees for the genetic testing will still need to be paid. A key challenge is to determine how the test report should be handled so that the results are not inadvertently disclosed to the patient. With electronic medical records, results are readily accessible to other providers and may even be obtained directly by patients through patient portals. It is important in pre-test counseling to make patients aware of these issues regarding availability of results in their medical records.

When a Patient Declines to Inform Other Family Members

Ethical issues can arise when a patient with a neurogenetic condition refuses to disclose the diagnosis to other at-risk relatives. This failure to disclose can deprive the at-risk relative of information beneficial for their healthcare, reproductive and life decision-making. Non-disclosure can be particularly problematic if a physician is caring for at-risk relative(s) in their practice unbeknownst to the patient and the relatives. Given HIPAA legislation and

confidentiality, the physician cannot acknowledge or disclose that a family member has been seen.

Non-communication between relatives can have a significant impact on genetic testing and costs to the patient and the healthcare system. Depending on the neurogenetic condition, genetic testing can cost hundreds to a couple thousand dollars, but just a few hundred dollars if the familial gene mutation is known. If there are other affected relatives, patients should be encouraged to inquire about genetic test results to determine if the familial gene mutation is known prior to undergoing genetic testing. In turn, given the familial implications of genetic test results, patients should be encouraged to share their results with at-risk relatives, especially if they are the first to undergo genetic testing in the family. One can approach cases of refusal to communicate information to at-risk family members by asking the patient how s/he would have felt if the situation was reversed and family members had not shared their risk information. Ultimately, however, the patient's right to confidentiality and right to decide whom to disclose their medical information to is paramount.

Is There a Duty to Warn?

There have been a few legal cases regarding duty to warn about genetic conditions: Pate v. Threlkell (1995), Safer v. Pack (1996) and Molloy v. Meier (2004) (American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure, 1998; Burke and Rosenbaum, 2005). The American Society of Human Genetics issued a position statement on disclosure of familial genetic information in 1998 which addresses duty to warn (American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure, 1998). In general, neurogenetic conditions do not meet the criteria (i.e., a serious, imminent threat that can be reduced with a warning) to override the patient's refusal to inform at-risk relatives. Although many neurogenetic conditions are serious, inherited and at-risk relatives are identifiable, currently preventative and effective treatments are generally lacking.

Insurance Implications and Potential for Genetic Discrimination

An ethical consideration with genetic testing, especially predictive genetic testing for neurogenetic conditions, is how results could potentially be used by insurers in a discriminatory manner. It is important that patients be informed of potential insurance implications prior to testing so that they can obtain desired insurance coverage.

The Genetic Information Nondiscrimination Act (GINA), passed in 2008, does provide individuals with federal protections against genetic discrimination in health insurance and employment; however, life, long-term disability and long-term care insurance coverage are not protected under GINA (Hudson, 2011). Medical underwriting on the basis of current health status is not prohibited under GINA (Hudson, 2011). GINA does not apply to members of the military or veterans who obtain healthcare through the Department of Veteran Affairs or to health benefit plans for federal employees or the Indian Health Service (Hudson, 2011). Some patients may not be aware of these insurance implications and when informed, may subsequently decline testing or delay testing until after desired insurance coverage has been obtained.

Information about GINA can be accessed at www.ginahelp.org. The National Human Genome Research Institute has information and a searchable database of federal and state laws on genetic nondiscrimination in employment, health and other insurances (Genome Statute and Legislation Database: www.genome.gov/policyethics/legdatabase/pubsearch.cfm). Many US states have passed legislation that offers protections against genetic discrimination beyond what is provided by GINA, so both providers and patients would be advised to be aware of their relevant state laws. International laws can be ascertained through the HumGen database.

Anonymous Testing

Given concerns about potential insurance implications, patients may inquire about anonymous testing. This presents the clinician with the ethical dilemma about whether to a) inform the patient about how this could be accomplished and help facilitate such testing, or b) deny the patient's request. It also needs to be weighed whether it is best for the patient to be seen anonymously in the clinic under an assumed name and be appropriately counseled versus obtaining testing outside of a clinical setting, if available, through direct-to-consumer (DTC) genetic testing. After anonymous testing is performed, there are also issues regarding the fact that results will be placed in a created patient's record with no link to the actual patient. Anonymous testing has been done for Huntington disease (Mehlman et al., 1996; Visintainer et al., 2001) and there are some significant counseling considerations with this approach (Uhlmann et al., 1996).

What to Do When Ethical Issues Arise

Generally, the typical ethical issues that arise with neurogenetic conditions center on autonomy and non-maleficence. There can be competing rights to consider – patient's right versus relative's right, parent versus child preferences, "right to know" versus "right not to know." In such cases, it is important to consider the case from the different perspectives to identify the locus of decision-making and related ethical issues that need to be resolved.

When ethical issues arise, it is important to take the needed time and not rush to make a decision. To address the ethical issue, it should first be determined whether there are genetic testing practice guidelines for the neurogenetic condition. Practice guidelines can be ascertained by searching the literature, the American College of Medical Genetics and Genomics and other professional organization websites, MedGen (http://www.ncbi.nlm.nih.gov/medgen), National Guideline Clearinghouse (www.guidelines.gov) and for international policies, Eurogentest (www.eurogentest.org), HumGen (www.humgen.org) and Orphanet (www.orpha.net). Depending on the ethical issue, there may also be global guidelines that are not specific to a condition but instead are broadly applicable, for example, guidelines on testing children (Ross et al., 2013), adoptees (American Society of Human Genetics Social Issues Committee/American College of Medical Genetics Social, Ethical and Legal Issues Committee, 2000) and familial disclosure/duty to warn (American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure, 1998). Discussing the case and seeking input from colleagues and other clinicians with genetics expertise can be beneficial. An underutilized resource is requesting

input from ethicists at an institution, either a formal ethics consult or contact with an ethics committee (McLean et al., 2013).

Consulting with Genetics Specialists

When ordering diagnostic genetic testing for patients, neurologists should recognize the potential familial implications and either address these implications or refer the patient to a genetics clinic/genetics specialist for further discussion. Neurologists should only order predictive genetic testing on an asymptomatic patient if their team includes a specialist in genetic counseling (clinical geneticist, genetic counselor or genetics nurse) and otherwise should refer the patient to a genetics clinic (MacLeod et al., 2013). Resources for locating genetics clinics and specialists include the American College of Medical Genetics and Genomics, the American Board of Genetic Counseling, the National Society of Genetic Counselors, Orphanet, GeneClinics and directories in respective countries; these listed organizations have online searchable directories. There are also different companies that provide genetic counseling by phone with certified genetic counselors that can be ascertained through an internet search.

Key Emerging Issues

Direct-to-Consumer Genetic Testing

In recent years, direct-to-consumer (DTC) genetic testing companies were launched which offer genetic testing for different traits (e.g. athletic ability), ancestry, genealogy, nutrition status (e.g. assess need for supplements), carrier screening and genetic susceptibility testing for medical conditions (e.g. diabetes, heart disease). Genetic susceptibility testing has also been offered DTC for neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis (ALS), and prion diseases (Roberts and Uhlmann, 2013). DTC testing typically identifies low penetrant genes with very modest effects on disease risk. Of note, most of these DTC tests are not currently offered in genetics clinics and are not considered standard of care.

Advocates of DTC testing note that it provides consumers with privacy and full autonomy in making testing decisions since tests can be ordered without physician involvement, with the possibility of discrimination by insurers and others potentially reduced since results are not part of the medical record (Vayena, 2015). Its proponents also view DTC testing as empowering and providing personal utility (e.g., informing advance planning). In this view, current restrictions on genetic susceptibility testing—including a 2013 action by FDA against the leading DTC company *23andMe*—are seen as unduly paternalistic (Green and Farahany, 2014). However, in accordance with the precautionary principle of public health ethics, the medical genetics community has raised numerous concerns about provision of genetic testing in this format (e.g., American College of Medical Genetics, 2008; American College of Medical Genetics and Genomics, 2015a; Hudson et al., 2007). These concerns include the fact that most tests lack clinical utility, that the same tests can yield different results across companies, and that certain risks of testing may be accentuated when delivered in this format. These risks include the potential for providing misleading or scientifically unsound risk information that could lead to irrevocable or harmful health decisions,

unnecessary testing/medical procedures, and psychological distress (especially if the results are unexpected). Inaccurate interpretation of results may also result in false reassurance about disease risk. Given the relative lack of research in this area, however, it is not clear what is the actual likelihood or extent of such risks in a neurogenetic testing context (Roberts and Ostergren, 2013).

Providers may increasingly encounter patients who are either curious about DTC tests or who are bringing their own results into the clinic for interpretation. Clinicians may therefore be advised to learn more about DTC test options most relevant to their patient population. For example, dementia specialists may work with adult children of patients who are interested in finding out their *APOE* genotype and may have already undergone or expressed interest in DTC testing. Clinically, *APOE* testing is not recommended for asymptomatic individuals (Goldman et al, 2011). At this point, given the potential risks and the lack of proven benefits from DTC testing, healthcare providers generally should not be recommending such services for their patients.

Disclosure of Secondary (Incidental) Findings

The rise of genomic medicine has increased interest in the clinical use of genomic sequencing. As a result of undergoing genomic sequencing for another clinical indication, it is possible that gene mutations for neurogenetic conditions may be secondarily identified. The motivation to disclose secondary findings (previously referred to as “incidental findings”) is their potential impact on medical care. The obligations of both sequencing laboratories and ordering physicians in this situation have been the subject of intense debate in recent years. In 2013, the American College of Medical Genetics and Genomics (ACMG) provided recommendations, since revised, about what types of genetic information should be tested for and disclosed to patients, regardless of the original indication for the ordering of sequencing or age of the patient (American College of Medical Genetics and Genomics, 2013; American College of Medical Genetics and Genomics, 2014; American College of Medical Genetics and Genomics, 2015b; Green et al., 2013). Of note, the test results that the ACMG recommended for disclosure currently do not involve risk of neurodegenerative diseases, but pertain instead mostly to “actionable” conditions - heritable cancers and cardiac conditions. Nevertheless, the possibility of secondary findings with neurologic significance should be considered as part of the process of test ordering and in informed consent for genomic sequencing.

There are multiple ethical issues to consider regarding disclosure of secondary findings (Presidential Committee for the Study of Bioethical Issues, 2013) including beneficence (e.g. disclosure could benefit medical care), non-maleficence (e.g. potential for harm from disclosure and from non-disclosure), autonomy (e.g. issues of informed consent, such as allowing patients to opt-in or opt-out) and justice (e.g. limited access to sequencing given new technology and cost). In regards to secondary findings for neurogenetic conditions, many of the ethical issues to consider are those aforementioned in the chapter including: should these findings be disclosed, factors to consider (e.g. clinical actionability), what results should be disclosed if minors are tested, optimal timing if disclosed and psychological implications/potential for harm. For example, should secondary findings be

disclosed for conditions that result in cognitive and neurological impairment for which there is no effective treatment?

In addition, in the absence of a family history of a neurogenetic condition, interpreting the significance of a gene variant (also termed “mutation”), particularly if novel, can be challenging. Given reduced penetrance and variable expressivity that can occur with neurogenetic conditions, it may not be possible to predict if a patient will be affected and if affected, the timing, severity and disease course. Therefore, determining which secondary findings to disclose requires careful consideration given that patients may be informed about a secondary finding that causes distress, generates additional testing/procedures, and may ultimately turn out to be a variant associated with reduced penetrance (may not ever develop symptoms) or has significant phenotypic variability.

The Presidential Committee for the Study of Bioethical Issues issued a report in 2013 recommending that all individuals having genetic testing - clinical, research, direct-to-consumer - need to be informed in advance about the likelihood for incidental/secondary findings, what findings will or will not be disclosed and how they will be managed. (Presidential Committee for the Study of Bioethical Issues, 2013). Currently laboratories have varying policies regarding opting-in/opting-out of disclosure of secondary findings for genomic sequencing. Given rapid advances in genomic sequencing, disclosure of secondary findings is a topic that is currently being actively discussed by laboratories, researchers, clinicians and ethicists, and guidelines are still being developed and will keep evolving.

Using Genetic Testing to Determine Eligibility for Clinical Trials

There are several major AD prevention trials that employ genetic testing to identify eligible participants (Carrillo et al., 2013). For example, a major international clinical trial is now underway, testing two preventive therapies in ~1300 older adults who possess two copies of the APOE risk allele (ALZFORUM, 2014). Should such trials prove successful, genetic testing may then be a recommended means of identifying appropriate candidates for secondary prevention (e.g. anti-amyloid treatments). These developments would also likely raise ethical challenges. The informed consent issues and potential for genetic discrimination discussed earlier would be present, for example. From a justice perspective, there are concerns that these emerging treatments would not be equitably distributed across racial groups and social classes. There are also ethical dilemmas around resource allocation to consider when deciding whether, and to what extent, public resources (e.g., Medicare) should be used for expensive, promising, but unproven emerging biotechnologies (Pearson et al., 2013).

Use of Genetic Testing to Screen for Vulnerability

Genetic susceptibility testing for neurodegenerative diseases could ultimately be used to inform decisions beyond medical care. Some studies have suggested that *APOE* ε4 carriers are susceptible to dementia following traumatic brain injury, and related work has identified chronic traumatic encephalopathy as a particular syndrome resulting from repeated traumatic brain injury (DeKosky et al., 2010). These findings suggest that genetic testing

might ultimately prove useful as a tool to screen for vulnerability to neurological impairment in populations exposed to high-risk environments.

Some experts have called for longitudinal research programs to explore potential "public health benefits of *APOE* genotyping of high school athletes who intend to participate in impact sports or of prospective military personnel" (Gandy and DeKosky, 2012). If future research demonstrates and more precisely defines *APOE*-attributable risks, then genetic testing may one day be worth considering to inform parents' and young adults' decisions about playing contact sports (e.g., football, hockey, boxing) or engaging in certain types of military careers (e.g., those involving exposure to blast injuries from explosive devices). Given past ethical concerns in population-based genetic screening programs to inform suitability for military service (e.g., sickle cell testing in prospective Air Force pilots; see Markel 1997), care would need to be taken to avoid genetic stigmatization and discrimination against those who test positive, which could occur via misinterpretation and misapplication of screening results.

Conclusion

As this chapter illustrates, genetic testing for neurogenetic conditions can raise a number of ethical issues across the lifespan – from preimplantation testing to testing for dementia risk in older adults. Many neurogenetic conditions are inherited, and predictive genetic testing offers the opportunity to learn one's risk status. There are a number of factors to consider in decision-making about genetic testing, particularly when results will reveal the status of a family member who has not requested testing. Given rapid advances in genomics research and ever-changing genetic testing options, it can be a challenge for neurologists to stay on top of the latest developments in the field and their ethical implications for clinical practice. However, being mindful of the ethical considerations identified in this chapter and collaborating with clinicians with genetic counseling expertise will help neurologists proactively identify courses of action that enhance patient decision-making and reduce the potential for unintended harm.

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Table 1

Core ethical principles.

Ethical principle	Definition	Example
Beneficence	Taking positive steps to benefit the patient	Genetic testing aids in diagnosis and informs healthcare and life decisions
Non-maleficence	Avoiding harmful measures	Patient not subjected on basis of genetic test results to unnecessary or futile treatments/procedures that may pose risks
Autonomy	Promoting patient self-rule; freedom from interference	Provide patients with adequate information to make fully informed, voluntary decisions about genetic testing/care consistent with their values and beliefs
Justice	Fair distribution of benefits and burdens of medical care	Proven beneficial genetic testing options are made widely accessible

Table 2

Select recommendations from the predictive genetic testing guidelines for Huntington disease (MacLeod et al. 2013) that address ethical issues.

Informed, Voluntary Decision
“The decision to take the test is the sole choice of the person concerned. No requests from third parties, be they family or otherwise, should be considered.” (REC 2)
“The person must choose freely to be tested and not be coerced by family, friends, (potential) partners, physicians, insurance companies, employers, governments, etc.” (COM 2)
“Extreme care should be exercised when testing would provide information about another person who has not requested the test.” (REC 2.4) “This will arise when an individual(s) at 25% risk request(s) testing with full knowledge that his/her parent does not want to know his/her status. Every effort should be made by the counselors and the individuals concerned to come to a satisfactory solution of this conflict.” (COM 2.4)
Testing Children
Testing Minors: “It is recommended that the minimum age of testing be 18 years. Minors at risk requesting the test should have access to genetic counseling, support and information including discussion of all their options for dealing with being at risk.” (REC 2.1)
Testing Adoptees: “Testing for the purpose of adoption should not be permitted, since the child to be adopted cannot decide for him/herself whether he/she wants to be tested. It is essential, however, that the child should be informed about his/her at-risk status.” (COM 2.1)
Testing Patients with Possible Symptoms
“For participants with evidence of serious psychiatric condition, it may be advisable that testing is delayed and support services put into place.” (REC 2.5)
“Particular care should be taken with participants who are believed by the clinician to be showing early symptoms of HD; however, persons with evident but unacknowledged symptoms should not automatically be excluded from the test. Rather, they should be offered additional pre and post test support.” (COM 5.2.6)
Disclosure of Genetic Test Results
To Patient: “The results of the test should be given personally by the counselor to the person and his/her companion. In geographically remote areas the result session may be arranged by prior agreement with a clinician known locally to the participant. No result should ever be given by telephone or by mail. The counselor must have sufficient time to discuss any questions with the person.” (REC 8.5)
To Patient: “The participant has the right to decide at any time that the result shall not be given to him/her.” (REC 8.4)
To Third Parties: “As a rule, members of the counseling team or the technical staff should not communicate any information concerning the test and its results to third parties without the explicit permission of the person tested.” (REC 4.2)
To Family Members: “Only in the most exceptional circumstances (e.g. prolonged coma or death) may information about the test result, if so requested, be provided to family members whose risk is affected by the result.” (COM 4.2)
To Physicians: “Consent of the participant should be sought before sending a letter to any physician involved in their care (e.g. family doctor, neurologist, hospital physician” (COM 4.4)
Prenatal Testing
“Direct prenatal testing of the fetus where one of the parents is at risk but prefers not to know his/her carrier status should be considered where the couple requests this in pregnancy.” (REC 7.1.6)
“The couple requesting prenatal testing must be clearly informed that if they intend to complete the pregnancy whether the fetus is a carrier of the gene expansion or not, there Is no valid reason for performing the test. “ (REC 7.1.7)
“This is in line with the recommendation not to test minors. The child’s autonomy regarding his/her future right to decide whether or not to undergo a pre-symptomatic test is violated if pregnancy is continued in the case of an abnormal prenatal test result. The limiting of the couple’s autonomy and their right to freely decide on the action taken on the basis of the prenatal test result should be explained and clarified with respect.” (COM 7.1.7).
Preimplantation Genetic Diagnosis (PGD)
“Non-disclosure PGD should be discouraged.” (REC 7.2.3)
“Non-disclosure PGD raises troubling practical and ethical issues. First, in practice it will be extremely difficult to preserve the participant’s wish not to know. Second, the procedure creates difficult situations where reproductive physicians would be obliged both to offer more IVF/PGD cycles and to perform a sham transfer while the risk of having a child with HD will be (practically) zero.” (COM 7.2.3)
Genetic Discrimination
“Persons should not be discriminated against in any way as a result of genetic testing for Huntington’s disease.” (REC 2.3)

"Potential socioeconomic consequences, including employment, insurance, legal care of and access to children, adoption eligibility, social security, data security and other problems which may occur as a consequence of disclosing the test result or family history." (REC 5.3.5)