REVIEW ARTICLE

Ethical issues in susceptibility genetic testing for late-onset neurodegenerative diseases

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Funding information
NHMRC-ARC Dementia Research Development Fellowship, Grant/Award Number: GNT1102821

Genome-wide association studies have revolutionized our understanding of the genetic architecture of complex traits and diseases over the last decade. This knowledge is enabling clinicians, researchers, and direct-to-consumer genetics companies to conduct disease susceptibility testing based on powerful methods such as polygenic risk scoring. However, these technologies raise a set of complex ethical, legal, social, and policy considerations. Here we review and discuss a series of ethical dilemmas associated with susceptibility genetic testing for the two most common late-onset neurodegenerative diseases, Alzheimer’s and Parkinson’s disease, including testing in asymptomatic individuals. Among others, these include informed consent, disclosure of results and unexpected findings, mandatory screening, privacy and confidentiality, and stigma and genetic discrimination. Importantly, appropriate counseling is a deciding factor for the ethical soundness of genetic testing, which poses a challenge for the regulation of these tests and the training of healthcare professionals. As genetic knowledge about these diseases continues growing and genetic testing becomes more widespread, it is increasingly important to raise awareness among researchers, medical practitioners, genetic counselors, and decision makers about the ethical, legal, and social issues associated with genetic testing for polygenic diseases.

KEYWORDS
Alzheimer’s disease, bioethics, ethics, genetic testing, Parkinson’s disease

1 | INTRODUCTION

Genetics research has changed dramatically with the sequencing of the human genome, increasingly focusing on common diseases rather than single gene disorders. Complex disorders—such as diabetes, asthma, coronary heart disease or schizophrenia—result from the contributions of multiple genes and environmental factors. Over the last decade, genome-wide association studies (GWAS) and large-scale international genetics consortia have facilitated the discovery of thousands of associations between common genetic variants, and complex traits and diseases. This unprecedented progress in human genetics has enabled geneticists to conduct susceptibility genetic testing, using methods such as polygenic risk scoring (PRS), which estimate the relative genetic susceptibility of an individual to develop a disease based on their genetic profile.

Alzheimer’s disease (AD) and Parkinson’s disease (PD) are two highly debilitating late-onset neurodegenerative diseases. There is currently no cure or effective treatment for either, and their prevalence is expected to increase with population aging. Due to their considerable personal and economic costs, they pose an important challenge to societies around the world. Recent advances in biomedical science, and especially in neurogenetics, offer great hope for improving the prevention, diagnosis and treatment of both AD and PD. In particular, the power of genetic testing to identify individuals at...
increased susceptibility, and the ability to convey information about their relatives, creates a set of complex ethical, legal and social issues. Here, we aim to contribute to the debate, discussing issues related to the use of susceptibility genetic testing to assess genetic predisposition to late-onset neurodegenerative diseases, including its use in asymptomatic individuals, and its impact on different social spheres.

2 | LATE-ONSET NEURODEGENERATIVE DISEASE IN THE GENOMICS ERA

This first section briefly details the underlying mechanisms, pathology and genetic components of each of the two most common neurodegenerative disorders: AD and PD. In addition, we detail their incidence and prevalence, and the resulting global economic impact. Finally, we outline how genomic technologies have and will continue impacting the clinical handling of AD and PD.

2.1 | Alzheimer's disease

AD is a chronic and progressive disorder which leads to cognitive impairment and neuropsychiatric abnormalities. It is characterized by the accumulation of insoluble forms of the amyloid beta peptide (Aβ) and aggregation of tau proteins in wide areas of the cerebral cortex and the hippocampus.

AD is considered the most common neurodegenerative disorder, with an estimated prevalence of 10–30% in the global population over 65 years of age (Masters et al., 2015). While evidence suggests that sporadic AD affects all of the world's geographical populations in similar rates, high-income countries currently account for about half of the global prevalence (Alzheimer's Disease International [ADI], 2010). Importantly, dementia seems to be more prevalent in women than men (Masters et al., 2015). Alzheimer's can dramatically shorten life expectancy: median survival with AD is approximately 7.1 years after onset (Duthey, 2013). It is difficult to determine the independent contribution of Alzheimer's to mortality, as people suffering from AD often develop comorbid health conditions, related or not to the dementia process itself.

In 2010, the cost of dementia per year was estimated at more than 604 billion US dollars, representing approximately 1% of the global Gross Domestic Product (Alzheimer's Disease International [ADI], 2010; Duthey, 2013). High-income countries account for 89% of costs, whereas developing countries contribute under 1% to total worldwide costs (Alzheimer's Disease International [ADI], 2010). This discrepancy is explained by the disproportionate reliance on informal care (i.e., unpaid care provided by family) versus formal care (i.e., paid care provided by professionals) in different regions of the world. For example, 80–99% of people with dementia in urban areas in Mexico live at home, with this number increasing to 95–100% of patients in rural areas. In contrast, just 50–69% of people with AD live at home in all areas of Australia (Alzheimer's Disease International [ADI], 2010).

Based on predicted increases in the global prevalence of dementia, partly due to the aging population, costs of dementia in 2030 are expected to be 85% higher (Alzheimer's Disease International [ADI], 2010). Just in Europe, estimates of the future cost of AD predict a rise of 43% (Duthey, 2013). However, rising costs in developing countries are expected to be much sharper, because increased life-expectancy related to development will result in higher levels of AD. For example, the prevalence of dementia in Latin America is expected to rise by 435% by 2050 in relation to 2010 (Alzheimer's Disease International [ADI], 2010).

The vast majority of AD patients have the sporadic form of the disease, characterized by late onset; a small proportion of patients present early-onset inherited forms. Numerous genetic factors have been identified which determine the development of both sporadic and inherited Alzheimer's. Familial AD follows an autosomal dominant pattern of inheritance, involving three main genes implicated in the genesis of Aβ: presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (Verlinsky et al., 2002). Late-onset AD is much more genetically complex. The most common risk allele is found within the gene coding for apolipoprotein E (APOE), which is a major determinant of age of onset (Escott-Price, Shoai, Pither, Williams, & Hardy, 2017). Depending on its isoform (APOE2, APOE3, or APOE4), the risk of developing Alzheimer's increases or decreases. For example, one allele with the APOE4 polymorphism imparts a threefold increase in risk, whereas APOE2 is considered a protective factor (Masters et al., 2015). Other genetic determinants are involved in Aβ clearance pathways. Overall, approximately 24 common loci have been confirmed as susceptibility factors for sporadic AD, and several more show some evidence of association (Escott-Price et al., 2017; Kunkle et al., 2018). Importantly, the majority of known genetic contributing factors were discovered amongst populations of European ancestry, as is the case for many diseases. However, the rate of decline has not consistently been shown to be linked to APOE4 in nonwhite populations (Marden et al., 2016) and also differs across gender (Goldman et al., 2011).

Nongenetic risk factors for AD have also been identified. For example, diabetes, depression, smoking, and low levels of education are associated with increased AD risk (Masters et al., 2015). This highlights the relevance of environmental factors on the development and progress of complex disease.

2.2 | Parkinson's disease

PD is a slowly progressing neurodegenerative disorder known for affecting movement. The most common motor symptoms include tremors, rigidity and bradykinesia (Farlow, Pankratz, Wojcieszek, & Fouroud, 2004). Nonmotor symptoms and comorbid conditions are also prevalent, such as cognitive decline, depression, dysphagia, and symptomatic postural hypotension (von Campenhausen et al., 2011). PD is characterized by the loss of dopaminergic neurons in the substantia nigra, partly due to the accumulation of the α-synuclein protein (Poewe et al., 2017).

Parkinson's is the second most prevalent late-onset neurodegenerative disorder worldwide, with an overall prevalence of 1–3% of the over-60 population (de Lau & Breteler, 2006). Importantly, the number of PD patients is expected to double between 2005 and 2030 (Poewe et al., 2017). In contrast to AD, PD is more prevalent in men than women (Poewe et al., 2017). Evidence suggests that race and ethnicity might have an important effect on disease incidence (Poewe et al., 2017). However, it is currently difficult to discern whether these...
disparities are due to purely biological causes or sociodemographic factors related to health (Roberts & Uhmann, 2013).

PD is considered one of the costliest diseases in some countries (von Campenhausen et al., 2011), as it represents a high economic burden on the patients, their close family, and society as a whole. In the United Kingdom, the expenditure on PD is estimated to be between 449 million and 3.3 billion pounds every year (Findley, 2007). One important characteristic of a neurodegenerative disease such as PD is that the cost escalates in proportion to the progression of the disease. Direct costs, such as inpatient care and medication, increase with the development of comorbid conditions and the need for more healthcare resources. Similarly, the loss of independence of the patients results in increased indirect costs, shown by decreased productivity.

PD exists in several forms. Familial forms of PD are monogenic, inherited in autosomal dominant, autosomal recessive, or even X-linked patterns (Farlow et al., 2004). Sporadic or idiopathic forms of PD are more common and caused by the cumulative action of multiple genes. Studies confirm that some genetic variants responsible for familial PD also contribute to risk for sporadic PD (Poewe et al., 2017). For example, mutations in the LRKK2 gene represent a frequent cause of all forms of Parkinson's, accounting for 1% of sporadic cases and 4% of familial cases (Kalia & Lang, 2015). Risk-altering polymorphisms for sporadic disease can be found in PARK loci (initially discovered in familial PD), along with several other genes (Ibanez et al., 2017). Mutations in GBA, for example, are common genetic risk factors (Poewe et al., 2017). Overall, as many as 92 independent genome-wide significant signals have been identified (Nalls et al., 2017). Genetic factors contributing to disease are mainly associated with pathways related to α-synuclein proteostasis and degradation, mitochondrial function and immune regulation (Poewe et al., 2017).

In addition to genetic risk factors, environmental and lifestyle influences over disease development and progression are also relevant. For example, exposure to pollutants, physical activity, vitamin D levels, years of education, smoking status, and urate levels might influence overall risk for PD (Kalia & Lang, 2015). Arguably, this might be mediated by environmentally-triggered epigenetic changes in the nervous system (Poewe et al., 2017).

2.3 Impact of new technologies on the clinical handling of AD and PD

Accurate clinical diagnosis and treatment of neurodegenerative diseases such as AD and PD is a big challenge, given the complexity of said conditions. This is due in part to the difficulty of measuring and integrating all the factors that influence the expression of a disease across a patient’s lifespan, as well as differentiating these diseases from other disorders and common comorbidities. For example, over one third of clinically diagnosed patients with AD in a large clinical study were later found to be misdiagnosed (Masters et al., 2015). Similarly, a systematic review of accuracy of clinical diagnosis of Parkinson's estimated a pooled diagnostic accuracy of 80.6% in 11 studies over the past 25 years (Rizzo et al., 2016). Importantly, accuracy has not significantly improved in recent times, particularly diagnosis during the early stages of disease.

New technologies, such as neuroimaging and biomarkers, have emerged as essential tools to aid in the diagnosis of neurodegenerative disorders. Several biomarkers in cerebrospinal fluid (CSF), for instance, are promising diagnostic tools for AD, and could potentially enable diagnosis even before the development of clinical symptoms (Masters et al., 2015). Further, CSF-based diagnostic tests have also been suggested for PD (Poewe et al., 2017).

Genetic testing is another tool used to estimate susceptibility and aid diagnosis for several diseases, as well as an important means for research. Genetic tests are sometimes used to assess multiple diseases at once, instead of being targeted for a specific condition. Depending on the disease of interest and the purpose of the test, a couple of main questions must be addressed to establish its usefulness: which gene (or genes) should be analyzed, and whether the test has sufficient sensitivity and specificity (Cazorla, Aschie, Mitroi, Poináreanu, & Gorduza, 2016). In the case of complex diseases such as AD and PD, genetic testing often yields ambiguous results. This is partly because the effect of multiple genetic mutations can be altered by factors such as penetrance, expressivity, pleiotropy, epistasis or other known or unknown regulatory interactions (Roberts & Uhmann, 2013). In addition, even though current technologies are highly improved, there are still technical limitations which make results uncertain. For example, single-nucleotide polymorphism microarrays usually encompass common variants, but a considerable component of disease risk may come from rare or new variants. In fact, genetic testing for complex diseases assesses relative susceptibility rather than being a predictive method, meaning that it is mostly probabilistic and highly contingent (Arribas-Ay non, 2011).

Inheritance and susceptibility for AD and PD is difficult to predict, especially when only a single variant is assessed. Polygenic risk scores summarize genotype data to inform about the genetic architecture of a complex trait or a disease (Lewis & Vassos, 2017). Each score is based on known risk and protective alleles in genome-wide data, and it is calculated from GWAS summary statistics for the trait of interest (Lewis & Vassos, 2017). Discovery GWAS have estimated effects and effect sizes for hundreds of thousands of common variants, in addition to genome-wide significant loci. These additional polymorphisms also account for a fraction of the heritability of the disease and act in an additive manner (Escott-Price et al., 2017; Poewe et al., 2017). PRS is a powerful tool, precisely because it is able to account for the cumulative effects of genome-wide common variants (Ibanez et al., 2017). Indeed, it has been used to successfully identify at-risk individuals and estimate their overall risk.

The actual maximum prediction accuracy of PRS for AD has been estimated to be of 74%, compared to the 82% theoretical maximum that can be achieved by predictors of risk based on genotype data (Escott-Price et al., 2017). Mild cognitive impairment (MCI) is an intermediate stage in the progression from expected cognitive decline to dementia. Recently, an AD PRS was used to identify MCI in subjects in their 50s (Logue et al., 2018). Other AD PRSs, both including and excluding APOE, were able to predict the level and rate of memory decline (Marden et al., 2016). The average PRS in Parkinson's patients is indirectly proportional to age at onset (Escott-Price et al., 2015). A PD PRS has also been associated with motor and cognitive decline in
patients (Paul, Schulz, Bronstein, Lil, & Ritz, 2018), but not with levels of α-synuclein in CSF (Ibanez et al., 2017).

Ideally, PRS could capture the combined effects of genome-wide genetic variation in a single value, applicable in a clinical setting as an indicator of genetic susceptibility. Importantly, PRSs remain constant throughout life, which enables prediction from any age. Early identification of individuals at increased risk is imperative, because the pathological processes of AD and PD begin long before symptom onset. For example, abnormalities in biomarker measurements are seen as early as 20 years before AD onset (Masters et al., 2015). Additionally, PRSs could also be useful to assess several aspects of disease progression, as shown by some of the studies described above, which could help define disease prognosis and treatment options. Furthermore, a better understanding of the relationship between genotype and clinical phenotypes could also inform patient selection for clinical trials and other research endeavors to accelerate the development of precision therapies (Tan & Jankovic, 2006).

It must be noted that, even though PRSs are clearly attractive for clinical implementation, their accuracy may not yet be significant enough. PRSs will potentially become more informative with larger GWAS and knowledge of more variables (Ibanez et al., 2017). Conversely, other studies in AD indicate the contributions of any new findings are likely to be small and thus unnecessary for the overall genetic prediction of disease (Escott-Price et al., 2017). Either way, the accuracy of PRS may be improved by their combination with clinical and environmental variables (Lewis & Vassos, 2017), as well as more varied data sets to account for different ethnicities.

Neither PRSs nor any other forms of genetic testing are currently part of the routine diagnostic process for AD or PD. However, this might very well change in a not so distant future as the field continues evolving. The correct implementation of these tools will largely depend on the available legal safeguards worldwide. For the purpose of the ethical discussion in this manuscript, “positive results” and “risk-positive” will refer to high predisposition for a disease according to a genetic test.

3 | ETHICAL CONSIDERATIONS ASSOCIATED WITH SUSCEPTIBILITY GENETIC TESTING FOR NEURODEGENERATIVE DISEASES

The ethical debate about issues associated with genetic testing covers everything from the research which enables the creation of the technology to what uses are made of its results. Some relevant questions in the context of neurodegenerative disorders include: Under which conditions should patients, including asymptomatic individuals, have access to genetic testing? Could genetic testing for late onset complex conditions be mandatory under any circumstance? Should genetic test results ever be released to third parties, including the user’s family? How can individuals be protected from unfair treatment because of their genetic status? These and other questions can be approached from four basic ethical principles: autonomy, nonmaleficence, beneficence, and justice (Beauchamp & Childress, 2001). We shall discuss the ethical issues related to genetic susceptibility testing for AD and PD in respect to their corresponding principles (Table 1).

3.1 | Autonomy

Individuals are autonomous to the extent that they are able to make willing and reasoned choices and take action without outside control. In the context of genetic testing, respect for autonomy can be summed up in the right of individuals to make informed decisions on whether they wish to be tested, and what they wish to do with the results of said tests.

3.1.1 | Informed consent

Informed consent ascertains that individuals make decisions in a free, voluntary and rational manner. In the case of genetic tests, this is only achieved when users understand the purpose, risks, benefits, alternatives and possible outcomes of the test, treatment options, and their own right to confidentiality and voluntary withdrawal (World Health Organization [WHO], 2006). In addition, there should be disclosure of any potential conflicts of interest, such as financial interest or patents (Institute of Medicine Committee on Assessing Genetic Risks [CAGR], 1994). These same basic conditions apply for participation in research and clinical trials prior to or following a genetic test, with the addition of specific requirements to each case.

Meeting even just the minimum requirements for an informed consent form proves difficult with many recent technologies, including the use of susceptibility testing in which results may be ambiguous. It is important to note that both providers and clinicians who refer patients to testing, have the duty to find alternatives themselves when faced with obstacles applying the traditional mechanisms of consent; the right to be informed must be respected first and foremost (CAGR, 1994). Collective experiences on what users of these new technologies want and need to know will be fundamental to legally safeguard their autonomy (Roche & Berg, 2015).

It is important to emphasize that there exists an intrinsic power imbalance in situations where genetic testing is involved. Participants in a clinical trial, for example, have less technical knowledge than the researchers, placing them in a position of vulnerability. This imbalance may be aggravated when taking into account the gender, ethnicity, socioeconomic status, or other social conditions of a subject. AD and PD patients in particular are vulnerable given their dependency on others. Similarly, asymptomatic individuals wishing to test their susceptibility to AD or PD might do so because of known family history, placing them in a position of emotional and mental distress even before the test. Furthermore, some patients likely to be tested for susceptibility to a neurodegenerative disease may already be suffering from cognitive difficulties, compromising their full understanding of the test (Roberts & Uhlmann, 2013). This kind of compromised autonomy increases the preexisting power imbalance. How can the fully informed consent of agents with decreased autonomy be ensured, or should their use of genetic tests and participation in research be limited? According to the International Declaration on Human Genetic Data, genetic testing of children or adults unable to consent is only ethically acceptable if (a) the results have important implications for the health of the individual and (b) the test takes into account their
best interest (United Nations Educational, Scientific and Cultural Organisation [UNESCO], 2003). In reality, the complete exclusion of these groups from research and denial of health services could be considered a form of discrimination. Particularly in the case of AD and PD, exclusion of individuals even on early stages of disease would limit studies specifically targeted to ameliorating their condition. AD and PD patients with a compromised capacity for free consent should be protected against abuse, and their personal integrity respected (UNESCO, 2005).

Underage individuals are considered agents with reduced autonomy, and there are further ethical dilemmas specific to genetic testing of children. However, as susceptibility testing for AD and PD renders only probabilistic results and there are currently no cures of preventive measures available, we argue that there are currently no benefits to a child knowing their genetic susceptibility for AD or PD (Goldman et al., 2011). Furthermore, results might trigger anxiety or depression in the child, or even cause a sense of guilt in the parents due to the hereditary component (Cozaru et al., 2016). Therefore, genetic testing for AD and PD should be avoided for underage individuals. This point should be reconsidered in the future, when and if more treatment options are available, or when predictive technologies are more accurate.

### 3.1.2 Disclosure of results and unexpected findings

Individuals have the right to decide what they want or do not want to know about the results of a genetic test. This right is protected by national and international legislation around the world (Pont-Sunyer et al., 2015). In the case of genetic tests that provide information about susceptibility for multiple disorders at once, the assessment of the risks and benefits of learning a result could differ between those relevant to the original purpose and secondary findings. Furthermore, the decision to know would probably depend on the nature of the secondary finding (Roche & Berg, 2015).

Due to the complex nature of AD and PD, we would propose the following recommendations regarding disclosure: First, individuals should be made aware of their right not to know; even when they have specifically decided to take a susceptibility test for AD or PD, they retain the ability to change their decision of knowing. Second, given the lack of actionability for such diseases, we argue there is currently no justification to override a preference for nondisclosure. When and if this situation changes in the future, we would argue that, since health is defined as more than just physical well-being, an individual’s informed analysis of what constitutes their own well-being should prevail either way. Third, in order to avoid issues with unexpected findings, we propose that these diseases be considered exclusively in specifically targeted tests. Alternatively, we argue that these diseases should, for now, be excluded “by default” from multiple disorder susceptibility tests. Individuals wishing to know their risk status should explicitly request to “opt-in”, with the condition that they are given full information of what these particular diseases entail, ideally accompanied by genetic counseling.

Nondisclosure can work differently in a research setting (i.e., clinical trials), in contrast to patients being referred to a genetic...
test by their clinician or choosing to take one privately. Importantly, new forms of sequencing make it difficult to clearly define "unexpected" or "incidental" findings in these contexts (Christenhusz, Devriendt, & Dierickx, 2013), in turn obstructing disclosure guidelines.

A relevant situation regarding disclosure in research is the case of prevention trials. This kind of trial consists of studying subjects who present risk markers but who show no symptoms of disease. For example, patients with REM sleep behavior disorder (RBD) are extremely interesting subjects for Parkinson's prevention research (Postuma, Gagnon, Bertrand, Génier Marchand, & Montplaisir, 2015). A pool of RBD patients might be tested for genetic susceptibility and included in a trial. The dilemma arises from the fact that people who wish to participate in a trial do not necessarily want information about their genetic status.

Enrollment protocols in prevention trials are said to be blinded when they accommodate the choice of not knowing (Kim, Karlawish, & Berkman, 2015). For example, they include risk-negative subjects in the study so that participation does not automatically equate to being a carrier. In contrast, transparent enrollment protocols do not consider the option of nondisclosure, and most trials of these type only involve risk-positive subjects (Kim et al., 2015). Some critics of transparent enrollment pose that such protocols are coercive, arguing that blinded enrollment is a requisite for autonomy. Nevertheless, others argue that blinded enrollment is not ethically required, and point out that transparent protocols could in fact be of greater benefit, as it spares risk-negative subjects from the burden of participation without any personal gain (Kim et al., 2015). This last argument might hold more weight when at-risk individuals are defined solely by genetic susceptibility, instead of presenting other markers. That is, looking for PD risk-positive subjects in a general pool of individuals instead of RBD patients, for example.

Regarding disclosure in research settings, we argue that participation in research trials can be an altruistic act and individuals should be allowed to participate, whether or not there is a personal gain. It follows that their decision not to know should be respected, especially for unactionable disorders such as AD and PD, considering the trial might not work or they might be placed as a negative control. In the particular case of prevention trials, we find no justification for transparent enrollment protocols, as they disregard these principles. Finally, updated mechanisms of consent should be introduced in clinical trials to deal with new technologies. There need to be standard guidelines to regulate the type of information that should be revealed and how this information should be provided to participants. At the present time, we argue that AD and PD should be uniformly classified as unactionable, and should be excluded from genetic tests used in research for other disorders.

### 3.1.3 Mandatory population screening

Genetic screening is defined as large-scale systematic testing offered within a program intended to detect genetic characteristics in asymptomatic individuals (UNESCO, 2003). There is no inherent moral argument in favor or against genetic screening and monitoring; instead, its value depends on how tests are carried out and how the results are used (Congress of the United States Office of Technology Assessment, 1983). According to the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes (AP-GTHP, 2008), the following criteria must be met before any genetic screening program is implemented: (a) independent evaluation of its ethical acceptability; (b) approval from the competent body; (c) the program is recognized for its health relevance for the whole population or section of population concerned; (d) the scientific validity and effectiveness of the program have been established; (e) appropriate preventive or treatment measures in respect of the disease or disorder are available; (f) appropriate measures are provided to ensure equitable access to the program; and (g) the program provides measures to adequately inform the population or section of population concerned of the existence, purposes and means of accessing the screening program as well as the voluntary nature of participation in it. Additionally, the program should be supported by public education and genetic counseling (WHO, 2006).

While it is recognized that the decision to participate in any genetic test must be voluntary, some decision-makers might argue in favor of a mandatory testing in some cases. This is due to the fact that it is a minimally invasive procedure whose results could contribute to better resource allocation and more efficient public health planning. The risk of late-onset neurodegenerative disorders is already clear in terms of increasing social and economic burden, following the rise of prevalence of these conditions in coming years. This suggests that mandatory genetic screening might be collectively beneficial, and this could arguably outweigh the culture of individual rights inherent to autonomy (CAGR, 1994).

However useful, mandatory screening for AD and PD raises further ethical dilemmas. Even if such a measure is taken in order to inform policy-makers and health programs, what information and feedback should be returned to the individuals? This relates to the issues of disclosure mentioned above. Furthermore, current epidemiological data regarding prevalence of neurodegenerative disorders is arguably sufficient to inform public health decisions. Therefore, any population screening programs targeting AD and PD are only justified if their purpose is directing individuals to early action. For example, assessing PRS in an entire population would enable the identification of individuals in the highest and lowest percentiles of risk for developing particular diseases, so that public health programs can strategically invest on those who need it: individuals with a high PRS might be offered regular screening, referred to clinical trials, encouraged to change modifiable behaviors to decrease risk, or receive early treatment when available (Lewis & Vassos, 2017). Importantly, all these measures should be readily available to all the population before a mandatory screening takes place and individuals receive feedback regarding their genetic status. Given that this is not presently true for AD and PD—current data regarding risk-reducing behaviors is uncertain and evolving, and treatment is unavailable—we would find it hard to argue in favor of screenings.

A particular type of mandatory screening could be prenatal susceptibility testing. Testing for AD and PD is more technically challenging than for other conditions. Therefore, prenatal testing is usually strongly discouraged (Tan & Jankovic, 2006), especially if the user intends to carry a pregnancy to term regardless of the results.
(Goldman et al., 2011). In fact, requests for prenatal diagnosis of late-onset diseases are uncommon (Farlow et al., 2004), which indicates that a mandatory program would not be well-received by the public. However, these views might change as technologies become more reliable. For example, preimplantation genetic diagnosis has already been used to ensure the implantation of familial AD risk-free embryos (Verlinsky et al., 2002). Importantly, the perception and ethical soundness would depend on whether a screening program was widespread or specifically targeted to couples with known genetic risk or family history of neurodegenerative disorders. That is, if there was additional evidence to support a prenatal diagnosis or not.

The issue of prenatal screening is further complicated by the possibility of abortion. As there are currently no preventive measures available for AD and PD, the question arises if prenatal testing is a way to avoid the birth of particular individuals with specific risk alleles, rather than to prevent the conditions themselves (CAGR, 1994). Medical professionals have many different perspectives regarding genetic testing which could influence the termination of a pregnancy (Farlow et al., 2004). Regardless of personal beliefs, in countries where the legal right to elective abortion has been granted, selective abortion is a viable option.

It is important to note that legal rights do not resolve the related ethical dilemmas. Selective abortion in these cases is based on maternal considerations of the future child's quality of life (Post, 1994). While it is exclusively a woman's choice to terminate a pregnancy, several factors can contribute to the decision. There is a great variation in what people regard as a worthy and healthy lifestyle, which can be influenced by possible stigma toward disease and limited understanding of genetics. AD and PD are conditions with variable expressivity, uncertain manifestation, and generally late onset times, which makes it difficult to establish a solid moral argument in favor of selective abortion.

Mandatory prenatal screening for a nondeterministic predisposition for PD or AD could be viewed as a form of discrimination, even without considering the extreme of mandatory abortion. If the only aim of a mandatory screening program were as a warning, legislating against selective abortion based on the results could be a necessary protection against discrimination. However, that would limit women's right to choose. The answer would be to provide thorough information about the implications of a risk-positive result, particularly for couples with a clinical or family history of AD or PD (Brazier & Cave, 2011).

Even with the safeguard of information, it is still difficult to justify a mandatory screening program, regardless of whether it is planned for adults or as prenatal testing. This is partly due to the fact that even the most advanced genetic diagnostic techniques like PRS are insufficient to determine whether or not an individual will definitely develop AD or PD. Even though it is undeniable that the onus of caring for patients with AD and PD will greatly affect future generations, other currently available information should, in our opinion, be enough to push decision-makers to preventive action. When the time comes, it will be important to note that some societies value collective over individual benefits because of their cultural context, and this should be taken into account when weighing the ethical merit of such measures.

### 3.1.4 | Privacy and confidentiality

According to international declarations, a person's biological information, including human genetic data resulting from a test, must be held confidential in the conditions set by law and should not be disclosed or made accessible to third parties (i.e., employers, insurance companies, educational institutions, or the family) (UNESCO, 2005). Additionally, individuals are granted the right of respect for their private life, in particular to protection of their personal data derived from a genetic test (AP-GTHP, 2008). The only exception to these rights relates to cases when the person concerned has provided prior, free, informed and express consent for disclosure.

Challenging these ideas, some argue that genetic testing not only reveals the risk of an individual, but also indirectly that of blood relatives, raising the question of how personal genetic information actually is. A positive result can have considerable consequences for spouses (i.e., reproductive decisions) and other members of the patient's close social context (e.g., potential caregivers). As such, disclosing genetic susceptibility results might be considered a moral obligation. However, ethical reasoning should be made in the context of the genetic complexity of a specific condition (Arribas-Ayllón, 2011). In the case of AD and PD, for which genetic tests are largely probabilistic, there is currently no clear benefit of disclosure to family members.

Although all genetic information falls under the umbrella of protection mentioned above, it is worth discussing that, as discussed, AD and PD represent specific ethical issues linked to the probabilistic nature of their genomics. Derived health data from a genetic test in these cases will not necessarily determine the future onset of a neurodegenerative disease, which could make this information less sensitive than, for example, genetic data related to monogenic disorders. Being probabilistic, genetic data related to neurodegenerative diseases remains difficult to regulate, and the doubt also arises of who will decide when the probability has turned into a declared neurodegenerative disease, even before onset, and how that relates to data protection. Importantly, data-sharing approaches should be established in order to encourage joining efforts favoring research and protecting the interests of those affected by the disease, also taking into account the degree of such affection at the same time.

Finally, determining the scope of a right to health privacy within neurodegenerative diseases will prove to be challenging. We have already discussed the potential benefits of inclusion of these disorders in population screenings, thus challenging a right to health privacy in this regard. However, the fact remains that the promise of social long-term benefits might not be sufficient justification for disregarding the individual right to choose, especially given the nature of genetic information. Experience and the increasing debates will most likely direct future guidelines in this matter.

### 3.2 | Nonmaleficence and beneficence

Respecting choice is important but not sufficient when it comes to the ethical treatment of people. Efforts should also be made to secure their well-being and protect them from harm (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [NC-PHS], 1979). In this sense, nonmaleficence and
beneficence are closely related concepts dealing with the principles of maximizing benefits while minimizing risks (UNESCO, 2005). These principles are relevant primarily to the interpretation of the results of a genetic test, and the disclosure of this information to third-parties.

3.2.1 | Stigma and genetic discrimination

Indiscriminate access to medical and genetic information could give rise to different forms of discrimination and other risks to the individual. Knowledge of a person’s genetic status can cause stigma depending on their context. For example, in some low- and middle-income countries, dementia is often regarded as a normal part of aging (Alzheimer’s Disease International [ADI], 2010). However, a known positive result for AD or PD in other contexts could lead to the individual being belittled, even before the appearance of symptoms.

Beyond stigmatization, the disclosure of a person’s genetic information can lead to discriminatory behavior. Genetic discrimination involves the differential treatment of a person on the grounds of their actual or presumed genetic differences, known either through genetic testing, family history, or even information about the communities they belong to (Otlowski, 2005). Several international legal instruments prohibit any form of discrimination based on genetic heritage in a way that infringes a person’s basic human rights and fundamental freedoms, or for purposes that lead to the stigmatization of an individual, a family, a group, or a whole community (AP-GTHP, 2008; Convention on Human Rights and Biomedicine, 1997; UNESCO, 1997; UNESCO, 2003; UNESCO, 2005).

Genetic discrimination causes disadvantages with respect to access to health services, education and employment. In the United States, the Genetic Information Nondiscrimination Act (GINA, 2008) prohibits health insurers from denying coverage or charging higher premiums based solely on a genetic predisposition. It also prohibits employers from using a person’s genetic information as a factor in decisions such as hiring, firing, assigning jobs, or any other terms of employment. Finally, it prohibits employers from requesting, requiring, or purchasing genetic information about their employees and their family members (Hudson, 2011). A number of developing countries have also introduced legislative measures to protect citizens against discrimination and stigmatization related to medical conditions and genetic status (WHO, 2006).

Importantly, only a small percentage of people in surveys express concerns over third-party access to their genetic status regarding late-onset neurodegenerative disorders (Neumann et al., 2001). Indeed, it is essential to determine the likelihood for abuse to occur. For example, several events would have to take place for genetic discrimination to occur in the case of a patient who undergoes testing to determine susceptibility to AD or PD. First, the test would have to prove a high degree of genetic susceptibility to the disease for it to be relevant. Then, a potential employer or insurer would have to ascertain that a test has taken place and to somehow access the information (Brazier & Cave, 2011). For the latter to happen, considering the data protection safeguards internationally regulated, it would most surely have to be the patient the one to disclose such result. Finally, the consequence would have to end up in the patient being turned down for a job, or having insurance refused.

Even though it appears that information about conditions such as AD and PD is perceived as less sensitive, we argue that this might be mostly due to the fact that usual onset does not occur in the economically productive population. Considering that the aging population will lead to overall later retirement, it is possible that AD and PD will increasingly overlap with productive ages. Therefore, these diseases will arguably become more relevant for employability and, consequently, genetically susceptible individuals more vulnerable to discrimination. In the case of discrimination in insurance, current legislation primarily covers health insurance, and not long-term care insurance or other domains which are more relevant to AD and PD (Roberts, Christensen, & Green, 2011). Therefore, even though genetic discrimination seems currently unlikely, we argue that measures must still be taken to protect genetic information related to these diseases because of their overall sensitive nature and probable future consequences.

3.2.2 | The importance of genetic counseling

A great concern of genetic testing is the impact on the individual's self-image. Unlike infectious disease, genetic disease can be considered a part of the patient’s intrinsic identity, leading to self-classification as “defective” (CAGR, 1994). A test confirming, or even suggesting, the future development of a neurodegenerative condition can be overwhelming for some patients. Genetic test results for AD and PD, particularly if unexpected, may trigger adverse psychological responses, including stress and severe depression (Goldman et al., 2011; The Michael J. Fox Foundation for Parkinson’s Research, 2018). Conversely, not having clear answers is also a source of anxiety (Cozar et al., 2016). Disclosure of genotyping information can actually represent a benefit for those negative, and even for some risk-positive individuals, as long as some constraints are established (Green et al., 2009). The main and most relevant requirement is the provision of appropriate counseling by trained professionals.

Genetic counseling is essential to preserve autonomy in the informed consent process prior to testing, and it represents the difference between favorable and adverse reactions to the results following the test. In the case of complex diseases like AD and PD, genetic counseling should be done on a case-by-case basis, in order to account for the context of the individual (Farlow et al., 2004). When proper post-test counseling is guaranteed, the risk of further psychological risk is minimized. Research demonstrates that using standardized counseling protocols after an AD susceptibility test ensures effective coping skills (Goldman et al., 2011). Similarly, asymptomatic testing for PD, when done with the appropriate genetic counseling, may be useful to ease the anxiety of an at-risk individual when negative, or help them cope with transient distress when positive (Tan & Jankovic, 2006).

Genetic counseling is also important to avoid unreasoned decisions stemming from misunderstood technical terms, including the meaning of susceptibility itself. For example, the results of genetic testing have been shown to influence a person's finances, reproductive planning, and interpersonal relationships (Cozar et al., 2016). Therefore, counselors should convey the limitations of genetic testing for AD and PD with the technologies currently available, as well as the incomplete knowledge regarding protective measures patients
might feel encouraged to take (i.e., behavioral changes thought to decrease risk for developing disease). Importantly, genetic risk information with proper counseling might encourage the purchase of long-term insurance. This is particularly relevant for neurodegenerative disorders, because patients are often placed in nursing homes and go through lengthy inpatient stays (Paulsen et al., 2013; Roberts et al., 2011).

It is important to note that genetic counseling becomes challenging in diseases such as AD and PD, in which knowledge is continuously evolving; there are constantly new risk loci being identified, as well as related environmental risk factors. It will become essential to develop complete and up-to-date databases which can serve as reliable references for genetic counselors.

### 3.3 Justice

The concept of justice encompasses both the access and contribution to genetic technologies. Distributive and contributive justice are relevant to public planning, including questions of fair allocation of limited resources, how to deal with competing needs, and how to ensure the accessibility to technologies.

#### 3.3.1 Diversity in clinical and biomedical research

Even though nondiscrimination is a key principle in human rights, health disparities are deeply connected to sectors of society which have been historically discriminated against (United Nations Office of the High Commissioner for Human Rights [OHCHR], 2008). In the past, research has failed to fairly represent minority populations in clinical trials, and in biomedical research specific to factors relevant to their health. The lack of diversity severely limits the overall understanding of pathology of diseases where risk differs amongst ethnic groups, such as AD and PD (Goldman et al., 2011; Marden et al., 2016; Poewe et al., 2017; Roberts & Uhrmann, 2013). Particularly, it hinders knowledge of the interactions between genetic status and certain environmental risks to confer a prognosis (Oh et al., 2015). To date, GWAS of AD and PD have been largely focused on populations of European ancestry, even though it is possible that the same genetic markers may not necessarily show the same effect in other populations. Racial diversity in GWAS could help improve the predictive capability of PRS (Marden et al., 2016), as well as ensure that these technologies can be accurately applied to people of diverse ethnicities. Efforts must be made so that all members of society should equally share in the burden of research (i.e., participating in a clinical study) and equally reap its benefits (i.e., having access to genetic testing).

#### 3.3.2 Availability and accessibility of genetic tests

Two essential requirements for a just distribution of healthcare are its availability and accessibility. The former refers to the sufficient quantity of goods and services, whereas the latter implies financial and nondiscriminatory access to healthcare. Accessibility also refers to the right to seek, receive and impart health-related information, without impairing the right to confidentiality of others (OHCHR, 2008).

Those with high levels of perceived risk (i.e., because of family history or caring for a patient) are most likely to pursue genetic testing (Wikler, Blendon, & Benson, 2013). Considering that the prevalence of neurodegenerative diseases will continue to rise, and more people will have close proximity to patients within their social environment, it stands to reason that the demand for susceptibility testing for AD and PD will increase. Taking that into account, some might argue that clinical and research settings obstruct, rather than facilitate, both the availability to and accessibility of genetic testing.

The marketing of direct-to-consumer (DTC) tests has emerged as an answer to the general public’s desire to knowing as much about their genes and their bodies as they choose, through simple and affordable services (Ramani & Saviane, 2010). DTC tests aid availability by increasing the supply of genetic tests in the market, which in turn helps lower prices to make these services more accessible. However, another key aspect to consider for a fair allocation of healthcare is the quality: What is the scientific and medical suitability of the tests, and whose responsibility it is to ensure it? Companies currently providing results related to AD and PD do so largely without the provision of direct genetic counseling by healthcare professionals, which puts users at risk of psychological distress if they fail to understand the significance—or lack thereof—of the results provided (Roberts et al., 2011). Furthermore, the results do not consider information relative to family history, rare genetic variation and environmental risks (Kaye, 2008). Finally, it is worth asking how up-to-date the information DTC tests use to determine relative risk actually is, considering that more recent independent genome-wide significant signals related to AD and PD are being reported constantly. Should these diseases be excluded from DTCs completely? Perhaps, but that would completely disregard consumer choice. Rather, stricter controls should be put in place for companies offering these kinds of tests. For example, requiring them to offer genetic counseling as part of their services, as well as have controls in place to assess the validity of tests before they are marketed.

Regarding the accessibility of information, we argue that it is imperative to design policies targeted toward increased scientific literacy worldwide. In the case of susceptibility testing for AD and PD, this entails more accessible information regarding genetics (i.e., heritability, genetic determinism), statistics (i.e., what does a probabilistic result actually mean), and medicine (i.e., what these diseases entail, possible and probable prognosis, currently available treatment options, etc.). We additionally argue that, even though there is some correlation between knowledge and the general attitude toward genetic testing, public perception is also defined by other factors, including social and cultural ones. Therefore, information aimed at changing stigma related to aging and mental health will also be necessary in many contexts.

In addition to widespread information for the general public, it is imperative that potential users of genetic testing are further guided by the medical community (Tan & Jankovic, 2006). However, before being able to properly educate others, professional healthcare providers must first and foremost understand: (a) how easily misinterpreted probabilistic estimates of risk can be in the absence of family history or information about environmental risks, and (b) that said misinterpretations can have varying harmful effects depending on several contextual factors of the patient. The fact remains that the understanding of risk amongst the medical community is exceedingly low (Green et al., 2009). For PRSs, the concept of genetic susceptibility
based on a continuous score, instead of on the presence/absence of a high-risk variant, also entails a paradigm shift for medical professionals in their understanding of heritable disorders (Lewis & Vassos, 2017). Sharing knowledge with laypersons is further hindered by the lack of education in areas like nonverbal and intercultural communication, or even lack of empathy to what a neurodegenerative disorder might mean for any given individual in a particular context. The remedy is to teach doctors how to communicate more effectively (Brazier & Cave, 2011).

In order to develop appropriate educational materials for both healthcare providers and the general public, the following must be taken into account: baseline knowledge of basic principles, interest in topics of genetics and statistics, and opinions regarding genetic testing (Falcone, Wood, Xie, Siderowf, & Van Deerlin, 2011). Additionally, existing preconceptions surrounding mental health and aging should also be considered. It is imperative to mention that the onus of providing said education falls mainly on public institutions.

### 3.3.3 Allocation of resources

Genetic testing raises questions of justice in terms of allocation of resources. The experience with DTC tests suggests that the demand for testing is considerable and might be even greater if costs decreased further. Will the increasing supply and demand of genetic tests for a growing number of conditions push governments to provide the service as part of a public health program? Indeed, individuals have a right to enjoy the highest standards of health, in a system which provides equal opportunity for everyone (OHCHR, 2008), but whether such a system should consider access to genetic testing is debatable.

In the case of AD and PD, taking a susceptibility test does not determine the outcome of a positive or negative prognosis. However, early diagnosis of at-risk individuals could enable the stratification of patients and, possibly, optimal placing in clinical trials according to their genetic status. The question is whether the chance of a more positive outcome, helped by a genetic test result, is sufficient to demand the accessibility of genetic testing, especially considering the implication of financial attainability. If there eventually exists a reliable therapeutic method for either AD or PD, would that signify a stronger argument? Even if prices for genetic testing decrease, cumulative costs would still represent a significant sum for public expenditure, especially if genetic counseling is also provided.

Additionally, resources are limited, and decision-makers need to take as many factors as possible into consideration when budgeting. For example, would widespread investment on genetic disease raise health costs? Or would it mean a decrease in budget for another area, such as infectious disease? Importantly, conditions with a hereditary component will have increased incidence in particular groups, in contrast to infectious disease which generally affects the entire population. If accessibility to genetic testing for AD and PD is ensured, some might argue that this benefits only certain populations with a predisposition, aggravating inequity amongst these groups and “healthy” individuals. However, we argue that such inequities could be morally permissible, as they are in the benefit of the least well-off group.

In general, access to genetic testing could potentially improve the effectiveness and efficiency of public health policies and expand the delineation of the principle of justice. However, even assuming that public expenditure on genetic testing should be approved, we argue that testing for late-onset neurodegenerative diseases should presently be of low priority, at least until treatment is available or burden becomes more evident.

### 4 Conclusions

Beyond understanding the biology of disease, some of the ultimate goals of research in genomics include advancing the science of medicine and improving the effectiveness of healthcare. Undoubtedly, integration poses great challenges. However, it is an ethical obligation to make the best possible use of scientific progress to advance society (Brand, Brand, & Schulte in den Bäumen, 2008).

In the case of genetic testing for late-onset neurodegenerative disorders, a plethora of issues arises, many of which are common to other complex diseases. In this manuscript we have established the importance of governments strengthening legislation to support the principles of autonomy, beneficence and nonmaleficence, and justice.

We argue that users of susceptibility genetic testing for AD and PD should be considered to be in a condition of vulnerability, particularly those who approach genetic testing because of a clinician's referral and those who participate in research. As such, strong measures must be taken to ensure that their decisions regarding what to do with their results are respected, and to protect them from any discrimination stemming from their genetic status. This includes the development of standardized regulations specific to clinical and research settings, as well as the regulation of DTC tests. Importantly, we argue that susceptibility testing for underage individuals should be discouraged in all three contexts, given the probabilistic nature of tests for these diseases and the current lack of actionability.

Due to the complex nature of AD and PD, and in order to avoid unnecessary issues with unexpected findings, we also argue that, ideally, they should only be included in multiple disorder screenings when individuals explicitly request them and with the support of a genetic counselor. This is particularly relevant in the context of DTC, as the provision of counseling is not currently taken into consideration overall. Appropriate genetic counseling is imperative to maximize the benefits of susceptibility genetic testing for neurodegenerative disorders, which is why we pose the importance of complete, up-to-date and accessible reference databases, in order to deal with the continuously evolving knowledge of these diseases. In addition, we also argue the importance of accessible information for the general public and improved training of healthcare professionals regarding topics of genetics and statistics. We assert that education is mainly the responsibility of public institutions.

Importantly, said institutions are also responsible for protecting genetic test users from discrimination. Even though data related to AD and PD might currently be considered less sensitive, we argue that measures must be taken now to avoid any future negative consequences for risk-positive individuals.
Regarding the potential benefits of including these disorders in population screenings, we argue that the promise of future benefits is not sufficient justification in this case, and the right to health privacy should prevail. This is mostly due to the fact that epidemiological data and other currently available information should provide enough information for decision-makers to design appropriate health programs that will reduce the increasing burden of AD and PD in the future. Similarly, we argue that public expenditure should not presently consider susceptibility testing for these diseases. Rather, public health actions should prioritize AD and PD in other ways, such as increasing investment in community care facilities, launching campaigns to educate the public, and taking the time to carefully analyze the implications of new technologies related to the diagnosis and treatment of neurodegenerative disorders.

It must be noted that what we have discussed is just the tip of the iceberg: we have not touched upon matters related to, for example, advanced requests for euthanasia and physician-assisted suicide after early diagnosis of neurodegenerative disease. Importantly, all of these considerations must also be taken into account in the ethical debate of these disorders.

Finally, even though evidence should be the base for science and health policy, trust will only be strengthened if public participation is an integral part of the discussion. We assert that it is imperative to bridge the communication gaps amongst researchers, clinicians, decision-makers, and the general public. We must maximize the benefits of a public debate enriched by the multiple moral and philosophical viewpoints present in the pluralistic society of today’s globalized world. Genetics research and technology will continue advancing our knowledge of human biology. Thus, it is pressing to engage in a discussion of its ethical, legal, and social implications in an interdisciplinary, open, and inclusive manner.

ACKNOWLEDGMENTS

MER thanks the support of the Australian National Health & Medical Research Council and the Australian Research Council through a NHMRC-ARC Dementia Research Development Fellowship (GNT1002821).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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