**The ethical implications of genetic testing in neurodegenerative diseases: A systematic review**

***A short running title:*** **The ethical implications of genetic testing**


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**Abstract**

**Background**: Availability of genetic testing in neurodegenerative disorders has developed rapidly. This growing ability is providing specific genetic information to individuals and, in turn, their families, raising ethical concerns. However, family members' perspective is a seldom-studied phenomenon.

**Aim:** The aim of this systematic review was to describe the ethical aspect of genetic testing in neurodegenerative diseases from the perspective of at-risk family members.

**Method:** A systematic review of data was performed in accordance with the PRISMA statement. The data search was conducted using the CINAHL, PubMed, and Scopus databases to identify original peer reviewed studies published between January 2009 and April 2019. A total of 24 articles were selected. The data were analyzed using inductive content analysis.

**Findings:** On the basis of the analysis, four central ethical implications were identified: i) decision-making in genetic testing as a dilemma: balance between autonomy and responsibility, ii) the individual's right to make a voluntary and informed decision for genetic testing**,** iii) conflicting emotions after knowing one's genetic status and iv) privacy and confidentiality of genetic information: the fear of genetic discrimination and stigma.

**Conclusions:** The findings of this review increase understanding about the central ethical implications of genetic testing in neurodegenerative diseases from the perspective of family members, and identify and underline outstanding needs for further research.

**Keywords:** genetic testing, ethics, neurodegenerative diseases, systematic review, family member, relatives

## Background

Neurodegenerative diseases, such as frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), familial (presenile) Alzheimer's disease (AD) and Huntington disease (HD), are a heterogeneous group of disorders that are characterized by the progressive degeneration of the central nervous system. These diseases also have a remarkable genetic inheritance and, especially, mutations that have an autosomal dominant pattern of inheritance raise ethical issues with testing (1–4). However, there are no disease modifying drugs available for these diseases. The possible emergence of treatment for these diseases would significantly change the ethics of genetic testing.

As the understanding of genetics in neurodegenerative disease becomes better understood, opportunities for genetic testing will provide tools for clinical diagnostics and, thus, testing will increase. Genetic testing for neurodegenerative disorders is usually performed for diagnostic purposes (diagnostic test) or to determine if a person, who has a family history of disease, is a mutation carrier and, thus, he/she is at risk to develop the disorder or could have an affected offspring (predictive testing) (5). In the diseases with an autosomal dominant pattern of inheritance, obtained genetic information reveals not only the genetic risk information about the individual, but also information about the risk for genetic disorder in his/her relatives. Access to genetic testing in clinical settings varies between and within countries due to the differences in regulation and legislation, as well as costs of testing and access to care. However, there is no clear understanding of how many at-risk family members choose to undergo the testing procedure (6).

The principles guiding the ethical conduct of genetic testing are respecting persons (patient autonomy), promoting the patient's benefit (beneficence), avoidance of harm (nonmaleficence) and justice (fairness in the distribution of available resources and facilities) (7). Respect for a person's autonomy implies an individual's right to privacy, voluntarily given informed consent and confidentiality of his or her personal information. In the context of genetic testing, principles of autonomy refer to an individual's right to make an informed and independent decision about whether they wish to be tested and then whether they wish to know the details of the outcome of the testing (8). Obtaining informed consent is integrated into the genetic counselling process (9) and includes, e.g., discussion of the purposes, potential benefits, risks and limitations of genetic testing (8). Genetic counselling is a communication process, aiming to help patients and their families understand and adapt to the medical, psychological and familial implications of the genetic contribution to specific health conditions. Privacy and confidentiality of sensitive genetic information is a complex and challenging issue, and failure to protect those rights can result in devastating effects for individuals and their families (8,10).

Beneficence implies the obligation to help and provide a benefit to others, while the principle of nonmaleficence implies the obligation to not harm others (7,11). These principles are typically topical when a person is considering participation in genetic testing that can have adverse effects and will reveal genetic information about oneself and one's family members. Justice in a genetic testing context requires that all individuals in similar situations are treated fairly and equally. It encompasses ideas of fair distribution of benefits, burdens, resources and outcomes (7).

When availability of genetic tests increases there is a great need to assess, what is the effect of these tests for patients' next of kin's. Especially when these tests are clinically useful for diagnostics but not necessarily always essential. Health care professionals play a key role in balancing the needs and rights of patients and their families (12,13). Although there is a large body of literature concerned

with ethical implications of genetic testing, the at-risk family members' perspective is still a seldom-studied phenomenon. Thus, the aim of this systematic review was to describe the ethical implications of genetic testing in neurodegenerative diseases FTD, CADASIL, HD, ALS and familial presenile AD from the perspective of family members. These diseases were selected because they comprise a group of progressive neurodegenerative diseases leading to dementia and eventually to decease. Disease course modifying drug is not available for any of these. In addition, practically these are the only diseases that present with the autosomal dominant pattern of inheritance (only a very small proportion of Alzheimer, so called "early onset Alzheimer).

The research question was as follows:

> What are the views of family members about genetic testing in neurodegenerative diseases?

## Methods

The systematic review was conducted in accordance with the PRISMA statement (14).

### *Search strategy and outcomes*

Literature searches were conducted in the Scopus, PubMed and CINAHL databases. Search terms were formulated based on the preliminary search in collaboration with a university librarian to ensure the validity of the searches. A two-step search strategy was used; first, an electronic search was conducted, and then, reference lists from all selected original studies were manually searched. The search terms used in the searches are presented in Table 1. The search was limited to studies published between 2009 and to the end of April 2019. The limit of 10 years was chosen because the field of genetic testing has changed rapidly in the recent years. No other limitations to the electronic searches were set in this stage.

The search strategy and selection process are presented in the PRISMA flow diagram in Figure 1 (14). The systematic selection process was carried out in steps and selection of the original studies was based on the inclusion and exclusion criteria. The inclusion criteria were: 1) focus on the ethical implications of genetic testing (pre-symptomatic testing or diagnostic testing) in neurodegenerative diseases (FTD, CADASIL, HD, ALS and familial presenile AD) from the perspective of family members, 2) peer reviewed articles, 3) reported primary research, 4) published in English and 5) studies using qualitative/ quantitative/mixed methods. The exclusion criteria were: 1) not corresponding with the aim of the study, 2) duplicate articles and 3) language other than English.

Through the database searches, in total 322 original studies were found. After duplications (n=133) were removed, the studies were screened by title (n=189), abstract (n=52) and full text (n=24) by two researchers (SMN and AH) individually. During the selection, any inconsistencies between the two authors (SMN and AH) regarding which literature to deem eligible for final inclusion were resolved through discussion with the third author (ES).

### *Data analysis*

The collected data was analyzed following the principles of qualitative inductive content analysis presented by Graneheim and Lundman (15). During the first phase of analysis, the 24 selected articles were read several times to provide an overview. After that, all the selected articles were extracted and tabulated according to author(s), year, countries, purpose, methods and main findings (Table 2). The next stage was to extract the meaning units, for example words or sentences. In the

third phase, the condensed meaning units were coded, and codes with similar contents were organized into subcategories and further abstracted into four main categories (Table 3).

## Results

### *Study characteristics*

The review comprised 24 articles. The studies were published between 2019 and 2014 (n=13), 2011 and 2013 (n=6) and 2012 and 2009 (n=5). The studies were conducted in North America (n=11), Europe (n=9) and Australia (n=4). From the selected studies, 13 were qualitative studies, nine were quantitative studies and two were mixed methods studies (Table 1). Their data collection methods used interviews (n=11), surveys (n=8), interviews and surveys (n=1), interviews and electronic patient data (n=1), electronic patient data (n=2) and text data (n=1). Studies focused on HD (n=19), ALS (n=2), CADASIL (n=1), and FTD (n=1), and 21 of them focused on predictive genetic testing and three on genetic testing generally. The number of participants varied, from a case study with one couple (including eight different interviews) to a survey with 1611 participants. Most of the studies focused on predictive genetic testing or did not clearly indicate whether the focus was a preventive or a diagnostic test. Therefore, in this article, the term genetic test is used to describe the phenomenon.

On the basis of the analysis, four central ethical implications were identified (Figure 2): i) decision-making in genetic testing as a dilemma: balance between autonomy and responsibility, ii) the individual's right to make a voluntary and informed decision for genetic testing**,** iii) conflicting emotions after knowing one's genetic status and iv) privacy and confidentiality of genetic information: the fear of genetic discrimination and stigma.

### Decision-making in genetic testing as a dilemma: balance between autonomy and responsibility

#### *Individuals' emotional aspects*

The motivation to undergo genetic testing varied within studies. The most common reasons related to individuals' emotional aspects were the desire to know and live without uncertainty, anxiety and fear (16–26) and time to make future plans and lifestyle decisions (16,17,20–22,24–26) such as starting family planning, and the desire to have children (16–18,20,22,27). A further reason to seek access to genetic testing was the lived experience of a family members' illness, such as growing up in a family with a genetic condition (17,19,20,24,28).

The main reasons for not pursuing genetic testing were the fact of there being no treatment for the disease being tested (24), recognizing the fact that one's genetic status was not going to change (20) and concern that the results of the test would cause psychological harm like anxiety, fear and depression (20,24). In addition, feeling unsure of how one would respond to the results, how the results would limit one's future (20), a fear of regretting having learned the results (17,28), prior belief of carrying a mutation gene, a fear of worrying about every possible symptom after positive test results and a wish to maintain hope were further reasons not to take the test (17).

#### *Responsibility towards others*

One identified reason to undergo genetic testing was to obtain genetic information for other family members at risk of having hereditary disease (16,17,21,22,25,26). Children's right to information related to their health and genetic status was described, as well as parents' willingness to be tested so that their children did not have to live with the uncertainty and fear (16,17,21,26,29). Further reasons were solidarity towards other family members who previously asked for testing, pressure from the

spouse or children (22) or being certain that information about the mutations status could improve the relationship with spouses, children and/or colleagues (28). One reason mentioned was that knowing the results of the gene test made it possible to prepare themselves and others for the future (20).

On the other hand, individuals were afraid of harming others by providing them genetic information, which may negatively affect their lives. Thus, the reasons for deciding not to undergo genetic testing were related, for example, to their desire to protect immediate family and relatives from harm, pain (23), worry and emotional consequences of positive test results (17,20,29). In addition, concerns about burdening family members with genetic testing (30) or feeling guilty about the hereditary nature of the disease, and giving their children a greater range of choices, were reasons not to undergo genetic testing (29).

## Individuals' right to make a voluntary and informed decision for genetic testing

### *Voluntary decision and conflicting interests within families*

Individuals' right to make a voluntary decision to undergo genetic testing and to have information about their genetic status was found to be a basis for ethical genetic testing (17,18,21,23). However, there was some evidence that a voluntary decision was threatened because of family members or health care professionals (23,28). For example, young people (16 or 17 years of age when tested) in a Mand et al. (19) study conveyed feelings of disempowerment, lack of control, and defeated expectations. They recalled the strain of what seemed to them to be a battle with health professionals and the emotional toll of the prolonged process they endured in order to access the information they desired.

The family relationships were put under pressure when family members did not share the same opinions on genetic testing, which caused conflicting interests within families (18,23,28,29). An ethically sensitive situation within a family arose when the at-risk parent did not want to undergo genetic testing or have any information about his or her genetic status, but the children (at 25% risk for HD) had decided to take the test. In this study, 60 percent of the 25% at-risk group and 73 percent of the 50% at-risk group went through the testing procedure. The violation of one's right not to know led to serious consequences, from depression to anxiety and even to a suicide attempt (18).

### *Enabling an informed decision: information and understanding*

Enabling an informed decision was seen as an essential element of safeguarding the autonomy of the individual when offering genetic testing for a genetic condition (18). Genetic counselling was seen as a prerequisite for the individual to ensure informed decision making on whether to take the test or not (18,31–33). It was seen as important that genetic counsellors helped the individual who was considering undergoing genetic testing and their family to find a satisfactory solution to help prevent adverse reactions. This included that the candidate and his or her family was well-informed about the testing options, alternatives, risks and benefits of the testing, results options and possible consequences to her/himself, but also to his or her family (18,32). It was considered important that family members at risk also had an opportunity to discuss the implications of their family member's testing if the candidate gave permission for the discussion (18).

However, limited understanding of the patient about the information provided to them prior to genetic testing was identified (24,28,30). Limited understanding was related to the hereditary nature of the disease, availability of genetic testing (30), the meaning and implication of their diagnosis for them and their families (18,30,33), as well as the testing process (24). Individuals' understanding was

influenced by their family experience (19,33), beliefs, pre-test genetic counselling, testing expectations (33) and follow-up information after the decision was made (24).

### *The need for more tailored counselling and long-term support*

Some concerns related to the inflexible and over-burdensome nature of the counselling process, which did not take into account an individual's specific circumstances and needs, was presented (34). Thus, need for more tailored and flexible counselling sessions, focusing more on each individual's needs and lived experience of genetically inherited disease, were desired (20,22,23,34–36). Moreover, it was found that lived experience of genetically inherited disease should be better taken into account in genetic counselling (19,20,22). The experience was that the individuals undergoing genetic testing often came from the families with a significant lived experience of the condition (19,20). These experiences included, among others, parental loss, parental dysfunction, traumatic experiences in childhood or adolescence related to family members' illness (20), and the significant emotional and practical day-to-day impacts of living with an unwell parent (19).

The studies showed that emotional support was needed in a long-term perspective (23,24,35,36). According to the Andersson et al. (36) study, health care professionals were seen to have an ethical and moral responsibility to provide support not only in the phase in direct connection with the actual genetic testing, but also a commitment to provide support to help the family deal with the long-term consequences of the testing. The long-term follow-up counselling after the delivery of results (24,35) was seen to be an opportunity to discuss the common concerns identified in mutation positive individuals, such as worries about discrimination and loneliness (35), and to have social support and understanding from someone who understood the condition (20,35). Often, social support and understanding about the disease among family members and those outside of the home was limited (20,35), so the long-term support offered by the health care professional was regarded as very important.

## Conflicting emotions after knowing one's genetic status

### *The impact of a positive test result: from catastrophic feelings and sadness to relief and lifestyle changes*

The selected studies demonstrated conflicting emotions of knowing one's mutation-positive status (27). For some, a positive result came as a devastating blow (31,33) characterized by anxiety, denial, anger, sadness, depression, suicide attempts, and relationship problems (19–21,27,31), while others were ambivalent or relieved after receiving a positive result (19,33). Even though the candidate was prepared for a positive test result, the bad news came as a shock (23).

The long-term consequences of positive test results were related to individuals' outlook and approach to life, and may have promoted lifestyle changes (19,35). The knowledge of being gene-positive for HD influenced the young adults' age-specific milestones—education and career paths, romantic relationships, and family planning. After testing positive, these young adults expressed an overall decrease in their desire to have children, due to the wish to avoiding transmitting the mutation gene to a child. They described their moral obligation to stop hereditary disease, and wanted to avoid putting a child through the experience of taking care of an affected parent and the fear of hereditary disease (35).

### *The impact of a negative test result: from relief and gratitude to guilt*

The conflicting emotions related to knowing one's gene-negative status were identified, and results showed that negative results of the genetic test did not always lead to uncomplicated happiness (19,23,27,32). The feeling of relief and gratitude for not carrying the mutation was described (19,32). The relief from anxiety was mentioned as the major and lasting benefit of the negative test results, which also became a motivator for making positive changes in life such as having children, investment in education, career development, taking care of one's health and improved relations with one's partner (32). However, some individuals who tested negative described feelings of shock and disbelief upon learning that they do not have the faulty gene. Some of the testees questioned the reliability of the test results (27).

For some individuals, favorable test results were accompanied by psychological reactions. Some had experienced the psychological pressure of needing to do something extraordinary in their lives, while others expressed feelings of guilt towards affected or untested siblings, resulting in sadness or depression (28,32). For those participants receiving good news, it was tempered by the knowledge that other members of their family may be facing a very different situation, such as siblings remaining untested or with a different test result (23,27). The hereditary disease was still part of their lives (27).

**Privacy and confidentiality of genetic information: the fear of genetic discrimination and stigma**

***How much information should be shared, and with whom?***

The results of genetic testing were described as being highly sensitive and personal. Patients were described as having the right to make an independent decision about what information, and with whom, they wanted to share (17,23,37). However, some confusion about how much genetic information should be shared, and with whom, was identified (32,36). Additionally, patients wondered how and when to tell others about the test results (32,35,36).

Discussion about genetic testing was often seen as a taboo within the family unit, which made it more difficult to discuss the aspects related to the genetic testing and its results (20,22), or even led to a situation where the positive test results were kept secret from family members (20). Informing the affected family members of the test results was seen as a difficult, frightening and complicated issue (32,35).

***The fear of discrimination and stigma***

Some concerns related to privacy and confidentiality of personal health information were addressed (37,38). Privacy concerns were related to the collection of, or access to, individually identifiable genetic data, whereas confidentiality concerns involved the disclosure of data previously entrusted to another. Fear of genetic-related stigma and discrimination arose from the loss of control over how genetic information was accessed or used (38).

Genetic discrimination—defined as the denial of rights, privileges, or opportunities or other adverse treatment based solely on genetic information (including family history)—was an important concern to patients and family members at risk for carrying a deleterious gene (39,40). The experience of being treated unfairly, as well as suffering the adverse consequences of knowledge of individual genetic risk, was experienced in the day-to-day lives of people with a positive diagnosis, or who were at risk for hereditary disease (38), and manifested in the workplace and employment, when seeking insurance, within social relationships, and during other daily encounters, such as in health care and public sector settings (18,37–40). Psychological distress was associated with genetic discrimination

(40). There was some evidence that individuals who learned they are at risk at a younger age or were highly educated were more likely to experience genetic discrimination (18,34).

The family and social circles were also the source of discriminatory experiences (28,38,40). After positive test results, some family members requested the individual not to have future contact with the family, or they abandoned the person, blamed them for the ills of other family members, or gave unwanted advice about personal decisions such as family and life planning (38). In countries in which relationships among different family members are close, stigma was prevalent also in the extended family (28,38). Due to the fear of genetic discrimination, many respondents kept their genetic status private, even from their close family (38).

## Discussion

### *Right to autonomy versus the familiar approach of genetic information*

The ethical debate related to the disclosure of genetic information to at-risk family members has received increasing attention (12,41–43). A familial approach to confidentiality, in which genetic information is conceptualized as confidential at the familial rather than the individual level, has been one of the key ethical question(12,41,43). According to present understanding, confidentiality of the patient's genetic information focuses on the individual approach, but some suggest that disclosure could be default and genetic information could be conceptualized as familial (12).

The familial and predictive nature of genetic information raises ethical issues regarding its disclosure to at-risk relatives (42). In the diseases with an autosomal dominant pattern of inheritance, obtained genetic information reveals not only the genetic risk information about the individual, but also his or her relatives. Previous studies have noted that upholding a patient's wishes and ensuring his/her right to autonomy, while also taking into account the at-risk family members' perspective, is reported as one of the most challenging aspects of genetic counselling (22,44). This review demonstrated that individuals who were considering a gene test reflected on it as both a personal choice as well as a responsibility towards others (16–25). Responsibility towards others included the obligation to provide genetic information to their at-risk family members and, on the other hand, the responsibility to protect them from the harm that this information might cause to them (17,20,23,29).

The ethical tension related to disclosure is often raised by a hesitation regarding how to best protect family members from harm, distress and the adverse effect of disclosure, rather than refusal to disclose for reasons that are self-centered (42). In neurodegenerative diseases, psychosocial effects may be more pronounced than, for example, in cardiovascular diseases (lifestyle has an impact), because the symptoms of neurodegenerative disorders can be very dramatic (e.g., personality and behavior changes**,** language problems, and problems with mental abilities), symptoms may start at a young age (3,4) and no disease-modifying therapies/treatments exist for these pathologies (5). The results of this review noted that patients had concerns related to the possible consequences of genetic information disclosure for family members' emotional welfare and, more broadly, family relationship. In addition, there was confusion about how much should be shared about their genetic information, and with whom (31,32), and how and when to tell others about the test results (31,32,35). Discussion about genetic testing with family members was seen as a complicated and difficult task, especially because this issue was often seen as a taboo within the family unit (20,22). Also, fear of discrimination or being rejected by family members because of hereditary neurodegenerative disease caused psychological strain, or even led to a situation where the genetic test results were kept secret from family members (20).

Health care professionals play a key role in balancing the needs and rights of patients and their families (12,13). They have a duty to discuss with the patient which family members are at risk and why, and to encourage these patients to communicate information about the genetic diagnosis to family members (45,46). However, in genetic testing, individual autonomy gains particular importance, and health care professionals should always respect individuals' right to autonomy and privacy. In addition, at-risk relatives' right to informational self-determination, involving the so-called "right not to know", which grants people the right not to be confronted with unwanted information about their personal matters, should also be respected.

To solve these complex ethical issues, patients should be offered access to high-quality genetic counseling. The aim of the genetic counseling is to provide objective information for each individual to make their own decision on genetic testing. Genetic counselling is a communication process, aiming to help patients and their families understand and adapt to the medical, psychological and familial implications of the genetic contribution to specific health conditions. The content and clarity of the information, and how this information is imparted, are very critical. Health care professionals should engage patients in a discussion about familial implications before genetic testing, help them to reach agreement in advance of testing (42) and give them the means to describe the impact of genetic information on the family. However, the process of communicating genetic information to family members is a challenging task (41,45,47), many relatives remain unaware of relevant genetic information and the possible impact on their own health (48), and it is often unclear whether relatives have been informed (12,47). Successful family communication depends on many factors, including pre-existing family dynamics and an individual's ability to give and receive complex genetic information (49). Furthermore, as the results of this literature review show, long-term support after genetic testing can help patients and their families to deal with the long-term consequences of the test. Long-term support from health care professionals was also seen as important due to the limited support and understanding among family members and those outside of the home, e.g. friends and colleagues (20,35).

### *Disclosing information and decision making*

The informed consent process is the main mechanism to protect patients and enable them to make autonomous decisions in genetic testing (7). Ideally, a well-considered decision is made by the patient and informed consent is obtained on the basis of accurate and detailed information. However, while healthcare professionals put much effort into ensuring patients' understanding about their impending genetic test, patients can still leave from genetic counselling relatively uninformed (50). The challenges were related to, for example, information provision and limited understanding [9,14,15,12,18] of the meaning and implication of diagnosis for patients and their families (18,30,33). It is also possible that some patients who are seeking access to genetic testing may already be suffering from cognitive difficulties, compromising their full understanding of the provided information.

Placing great emphasis on the informational aspect of genetic testing is not always the best way to support patient decision making in the informed consent process. It should be taken into account that decision making is always socially contextualized and also based on factors outside of information provision (50). Therefore, other factors that affect decision making, such as timing of the disclosure, capacity to understand given information, evaluation of the readiness of the relatives to receive such information, and cultural, emotional and social aspects, should also be taken into account, as concluded by this review in agreement with the previous studies (42). The factors influencing patient

decision making should be discussed during the informed consent process, because the decision may also be influenced by the factors that impair the realization of individual autonomy, such as factors related to family dynamics and pressure from others. Furthermore, this review highlights the need to better take into account individuality and individual needs, as well as the lived experience of a family members' illness during the genetic counselling and informed consent process (17,19,20,24,28). Instead of viewing consent as the passing on of decision-making capacity onto a (rational and autonomous) patient by the provision of information, consent needs to be seen as an on-going, collaborative process in which decision making is shared between health care professional, patient (50) and also, ideally, with family members.

***Genetic testing in neurodegenerative diseases is becoming more common, but there is still only little empirical research on its ethical implications***

As this systematic literature review shows, there is only a very limited number of empirical studies about the ethical implications of genetic testing in neurodegenerative diseases from the perspective of at-risk family members. Furthermore, the existing literature strongly focuses on the predictive testing for HD. A small number of studies have focused on genetic testing of other neurodegenerative diseases like FTD. Somewhat surprisingly, this literature review failed to find any research focusing on the AD. This is a very important finding because AD and FTD are the most common causes of dementia and their prevalence has been shown to increase in the future, making genetic testing an increasingly important part of diagnosis and management of the disease. Furthermore, an increased number of reported genes linked with these diseases highlights the need to better understand the ethical implications of genetic testing on familial AD and FTD. However, the complexity of genetic testing and genetic information, differences in regulation and legislation, the short- and long-term consequences of genetic diagnosis and its impact on at-risk family members raise unique ethical issues.

Increasing amounts of genetic information are generated, analyzed, shared, and stored in health care settings, wherein more genetic tests are becoming available for clinical use. However, the privacy and confidentiality of that information is one of the key ethical considerations. Genetic information is generally perceived as sensitive information because it may have implications for the health of individuals and their family members. In addition, this information may have remarkable social and economic consequences (10). As this review demonstrated, the privacy and confidentiality of genetic information was a concern for patients. The concerns were related to the collection, sharing and access to that personal information. In addition, patients were described as having confusion about how much genetic information should be shared, and with whom (32,36). Fear of genetic-related stigma and discrimination arose from these concerns (38). There is a need for more in-depth studies examining how individuals and their families who are at-risk for neurodegenerative disease understand the privacy of genetic information, and the ways in which they want their health information used and shared. Moreover, it would be important to explore more in depth which concerns they have related to privacy and confidentiality of genetic information. In addition, one unanswered question is how much an individual's genetic data and mutation-associated information should be disseminated to other health care professionals who take part in a patient's care (including other medical specialties).

To date, the use and ethical consideration of genetic testing in clinical work is based on the clinician's opinion. There is no comprehensive research data supporting the making of that decision from an ethical point of view. This underlines the need for both qualitative and quantitative research of ethical aspects, and specifically, the testing-associated burden on patients, their families and caregivers.

Furthermore, neurodegenerative diseases like ALS, HD and FTD are progressive diseases with no available, effective therapies to cure the disease. These diseases may result in a loss of the ability to communicate and care for oneself, may cause change of personality, and may cause a heavy burden on families due to increased care needs and worry. However, these diseases also have differences. For example, AD and FTD causes a decline in thinking and reasoning skills, changes in mood and behaviour, and impaired memory, and causes eventual dementia, while HD affects movements and may cause uncontrolled movements of the body. Also, HD can eventually lead to dementia, but the incidence of symptoms is different from AD and FTD. Thus, despite the similarities of the symptoms, it is possible that different ethical implications may arise when conducting genetic testing in FTD families compared with HD families. These differences may be related to, e.g., age of onset, disease progression, prognosis, FTD/ALS genes causal mutation vary between families (genetic heterogeneity, specifically HD has only one causal mutation) and the possibility of oligogenic inheritance (6). In the future, research should focus on the ethical aspect of purely dementia-related diseases such as FTD. In addition, there is a need for comparative research of the genetic-testing associated burden in various neurodegenerative disorders for gaining complete knowledge of the phenomenon. Attention should also be paid to diagnostic testing, because existing research is focusing mainly on predictive genetic testing.

### Strengths and Limitations

This systematic review contributes to a previously limited and fragmented body of knowledge and provides a synthesis of the ethical implications of genetic testing in neurodegenerative diseases. In addition, this review underlines the need for empirical research and identifies future research needs. This review has been performed in accordance with PRISMA guidelines otherwise no quality assessment has been performed for the selected studies (14). The topic has been a seldom studied phenomenon and therefore we wanted to include all the research related to the topic in the review. However, the selected studies have been published in peer reviewed scientific journals and the multidisciplinary group (SMN, AH, ES) discussed the selected studies and approved them for review unanimously.The search strategy, search terms, inclusion and exclusion criteria and databases were selected in agreement with an information specialist. Despite the use of an experienced librarian in the search for literature, the possibility exists that our search methodology, inclusion and exclusion criteria did not capture all relevant studies. Overall, the process of selecting and verifying search terms was a challenging process, and many preliminary searches were done prior to the final search in order to choose the best possible keywords. However, many duplicates were found in the three databases, so it can be assumed that the search terms used in this review were validly selected. A limitation may be that one criterion for inclusion was that the studies should have been published between the years 2009 to 2019. Therefore, some relevant literature may have been overlooked. In addition, the elimination of papers written in languages other than English might limit the range of observations.

## Conclusions

Ethical issues are of great importance when a person is considering undergoing genetic testing that will reveal genetic information about oneself and one's family members. Health care professionals have a key role in considering ethical implications of genetic testing in neurodegenerative diseases. However, the use and ethical consideration of genetic testing in clinical work is often based on the clinician's opinion. There is no comprehensive research data supporting the making of that decision. This review underlines the need for empirical research on ethical implications of genetic testing in neurodegenerative diseases and identifies future research needs. While genetic testing becomes more

widespread, it is increasingly important to raise awareness among researchers, medical practitioners, genetic counsellors, decision makers and the public about the ethical issues associated with genetic testing of hereditary neurodegenerative diseases.

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**Conflict of interest**

The authors declare that they have no competing interest.

**Ethical approval**

No formal ethical approval was needed for this study.

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Table 1: Search terms

| Search Terms | |
|---|---|
| Search keywords group 1: | "Frontotemporal dementia" OR "frontotemporal lobar degeneration" OR "c9orf72" OR "MAPT" OR "GRN" OR "CADASIL" OR "Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy" OR "Notch 3" OR "Huntington Disease" OR "HTT" OR “Early-onset Alzheimer*” OR "PSEN1" OR "PSEN2" OR "APP" OR "Amyotrophic lateral sclerosis" OR "C9orf72" OR "SOD1" |
| AND | |
| Search keywords group 2: | ethic* OR autonomy OR “informed consent” OR risk OR harm OR benefits OR justice OR privacy OR confidentiality |
| AND | |
| Search keywords group 3: | genetic testing" OR "predictive testing" OR “presymptomatic testing” OR “diagnostic testing” |
| AND | |
| Search keywords group 4: | "next of kin" OR relative OR family OR sibling* OR offspring* OR parent* OR spouses OR child* OR "care-givers" |

| Author(s) year, Country | Purpose | Methods | Focus | Main results |
|---|---|---|---|---|
| Andersson et al. (2016), Sweden (31) | to describe a young couple's long-term experiences and the consequences of a predictive test for Huntington's disease. | A descriptive qualitative study, interviews (n=18) | HD, predictive testing | The long-term consequences of HD and a predictive test were devastating for the family. The findings of this study highlight that a predictive genetic test should not be seen as an isolated event – but rather in a life-cycle perspective including the whole family network and focus on each individual's needs. |
| Bonnard et al. (2019), France (18) | to understand the differences in the motivation between 25% and 50% at-risk individuals to be tested and the consequences of "double disclosure", including parental reactions | Mixed methods study. A quantitative study included data from individuals (n=1611) tested in their centre (50% at-risk (n=1456) and 25% at-risk individuals (n=155). Qualitative dimensions were explored through a semi structured interview (n=4). | HD, predictive testing | Testees reported four adverse reactions of their parent (22%): one committed suicide and three became depressed. Thus, the impact of "double disclosure", a bad result for the person themselves and the transmitting parent was highlighted. |
| Bombard et al. (2009), Canada (40) | to assess the nature and prevalence of genetic discrimination experienced by people at risk for Huntington's disease who had undergone genetic testing or remained untested. | Quantitative study, survey (n=233) | HD, genetic testing | Genetic discrimination was commonly reported by people at risk for HD and was a source of psychological distress. Family history, and not genetic testing, was the major reason for genetic discrimination. |
| Dondanville et al. (2018), USA (20) | to explore the interaction between a young caregiver's perception of genetic risk, the caregiving experience, and thoughts about and plans for predictive testing | Qualitative study, a semi-structured interview (n=13). | HD, predictive testing | The genetic risk colors the caregiving experience by evoking feelings about the future and a potential diagnosis of HD, in addition to impacting plans for predictive testing. |
| Erwin et al (2010), USA (39) | to develop a comprehensive picture of the prevalence of genetic discrimination with inquiry into both instances of adverse treatment and instances where knowing one's genetic risk status may have some benefit in the employment or insurance contexts. | Quantitative study, survey (n=433) | HD, genetic testing | A total of 46.2% of the respondents report genetic discrimination or stigma based on either their family history of HD or genetic testing for the HD gene mutation. |
| Fanos et al. (2011), USA (17) | to explore participants' decisions of whether to learn results of presymptomatic testing or not; (2) understand the psychosocial impact of these decisions; and (3) assess preferences for receiving results by telephone or in person. | Qualitative study, a semi structured phone interview (n=20) | ALS, predictive testing | The findings of this study show that decision to learn results is an evolving process. In addition, reasons to learn and not to learn testing results were presented. |
| Goh et al. (2013), Australia (37) | to examines elements of genetic discrimination among an at-risk Huntington's disease population | Quantitative study, survey (n=60) | HD, predictive testing | Sixty eight percent of the participants reported feeling "Great benefit" from knowing their genetic test results. Reported benefits of knowledge included planning for the future, making decisions, and many individuals found meaning in active participation in the |

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| | | | | HD community and in advocating for themselves or families at risk for HD. |
| Gong et al. (2016), USA (35) | to explore if and how the knowledge of HD gene-positive status influences presymptomatic young adults' attainment of milestones, including education and career, romantic relationships, and family planning. | Qualitative study, a semi-structured interview (n=14). | HD, predictive testing | Results of this study demonstrate that 1) knowing one's gene-positive status results in an urgency to reach milestones and positively changes young adults' approach to life; 2) testing positive influences young adults' education and career choices, romantic relationships, and family planning; 3) young adults desire flexible and tailored genetic counseling to address needs and concerns unique to this population. |
| Hawkins et al (2013), Canada (34) | to understand and explore whether accessibility of predictive testing services is a barrier to testing | Qualitative study, interviews (n=33). | HD, predictive testing | The results of the study reveal that there are access barriers to PT that deter individuals from receiving the support, information and counseling they require. The inflexibility of the testing process barrier relates to the emotional and psychological accessibility of PT. |
| Holman et al. (2018), USA (26) | to (1) determine whether the average age when individuals seek presymptomatic HD genetic testing has decreased over time, (2) assess motivations for seeking testing, (3) explore whether there is a relationship between age and motivations, and (4) explore genetic counselors' perceptions of the shift in age. | Quantitative study. survey (N = 77) | HD, predictive testing | This study describes a small but statistically significant decrease in the age of individuals seeking presymptomatic genetic testing for HD over time. Additionally, three motivations for testing were correlated with age at testing. |
| Leite et al. (2017), Portugal (25) | to addresses the relation between illness representations, knowledge and motivation to perform the PST of subjects at-risk: FAP, HD and MJD, compared with subjects at-risk for HH. | Mixed method study, a semi-structured interview (n= 31) and survey data (N=174) | HD, predictive testing | It was in the subjects' metaphors that subjects best expressed what they felt regarding the disease and the situation of being at-risk for this disease. Family was their mirror and their source of learning. |
| Lewit-Mendes et al. (2018), Australia (24) | to examine the experiences of young people in families with Huntington disease. | Quantitative study, online questionnaire (n= 101) | HD, predictive testing | Young people in families with HD endure considerable emotional, social and practical burden secondary to having an affected family member and being at risk themselves. |
| MacLeod et al. (2014), UK (23) | to study experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment | Qualitative study, interviews (n=36) | HD, predictive testing | None of the participants expressed regret at having the test at a young age. Participants saw the value of pretest counselling not in facilitating a decision, but rather as a source of information and support. In HD the decision was autonomous and sometimes went against the opinions of parents/grandparents. Participants proposed more tailoring of predictive test counselling to the needs of young people. |
| Mand et al. (2013), Australia (19) | to (i) gauge the impact on young people of predictive testing before 18 years, (ii) identify factors that mediate the testing experience, and (iii) assess whether | Qualitative study, interviews (n=9). | HD, predictive testing | The results convey a range of benefits and absence of harms flowing from testing. The themes emerged from the interviews with young people were: (i) life before the test; (ii) the battle to be tested; and (iii) living with the knowledge. |

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| | evidence exists to support the central concerns raised in the existing literature with respect to testing young people | | | |
| Reyes et al. (2012), France (22) | to analysed the profiles and motivations of individuals at risk of CADASIL who asked for a PT and the neurological, cognitive and psychological modifications observed in applicants who got an unfavourable genetic test result. | Quantitative study, data from (n=33) individuals | CADASIL, predictive testing | This study highlights that a multidisciplinary and multistep procedure in genetic counselling testing appears useful to obtain the minimal harmful consequences of genetic testing. |
| Rivera-Navarro et al. (2015), Spain (28) | to analyse the factors that influence the decisions of adult children of persons affected with HD regarding predictive testing. | Qualitative study, focus groups interviews (n=27). | HD, predictive testing | The results of the study showed that over half of the participants were inclined to decline genetic testing. The main explanatory determinants for taking or not taking the predictive test were: Maturity of the individual at risk, which was directly related to age; Ability to cope with a positive test result; Experience of living with HD sufferers; Information about testing and psychological support; Attitude of the family; Social visibility of genetic testing; Personality and temperament of each subject at risk of HD. |
| Semaka et al. (2013), Canada (33) | to explore how individuals understood and interpreted their IA result. (intermediate allele (IA) | Qualitative study, a semi-structured interviews (n=29) | HD, predictive testing | Many participants had difficulty “Grasping the Grey”(i.e. understanding and interpreting their IA results) and their family experience, beliefs, expectations, and genetic counselling influenced the degree of this struggle. |
| Smedley and Coulson, (2019), UK (27) | to investigates how genetic testing is discussed within health forums | Qualitative study, a total of 337 messages written by 58 individuals | HD, predictive testing | Discussions examined three themes: deciding to be tested (enquiring about symptoms and starting a new family), preparing for the test (information seeking and attending appointments) and receiving the results (positive and negative results). |
| Smith et al. (2013), UK (29) | to examines of candidates’ decision-making in relation to the genetic test for Huntington’s disease | Qualitative study, semi-structured interviews (n=9) | HD, predictive testing | A key factor for participants was to do the right thing for their children. This factor presents a moral dilemma to participants and can direct them either towards or away from testing. |
| Scuffham and MacMillan, (2013), Australia (16) | to: 1) quantify the characteristics of those seeking presymptomatic testing for HD, 2) identify their motivations for testing, 3) quantify the waiting times between the various steps within the testing process, and 4) quantify the outcomes of testing at a large state-wide genetic testing center in Australia. | Quantitative study, a review of medical charts (n=152) | HD, predictive testing | The key findings of interest from this study are the differences in motivations for testing and the high proportion of those who tested positive. The most frequently cited reasons for seeking testing were "family planning", "plan future", and "need to know". |
| Surampalli et al. (2015), USA (21) | to assess uptake and decision making for predictive genetic testing and the impact on psychological well-being. | Quantitative study, questionnaires (n=29) | FTD, predictive testing | One third of individuals at 50% risk chose pre-symptomatic testing. Reasons for testing included planning for the future, relieving uncertainty, informing children and satisfying curiosity. At baseline, one quarter of the participants had high levels of anxiety. |

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|---|---|---|---|---|
| Winnberg et al. (2018), Sweden (32) | to explore the long-term (> 5 years) experiences after receiving predictive test results as a non-carrier of Huntington's disease | Qualitative study, semi-structured retrospective interviews (n=20) | HD, predictive testing | The results showed a broad variety of both positive and negative reactions. The most prominent positive reaction reported was feelings of relief and gratitude, of not carrying the HD mutation for themselves and for their children. Negative reactions on their psychological well-being were also described. Some had experienced psychological pressure of needing to do something extraordinary in their lives; others expressed feelings of guilt towards affected or untested siblings, resulting in sadness or clinical depression |
| Williams et al. (2010), USA (38) | to examine benefits reported by people with an Huntington's disease family history or those who have undergone predictive Huntington's disease testing, as well as the personal variables associated with perceived benefits. | Qualitative study, survey including narrative responses (n=74). | HD, predictive testing | Findings document that reports of genetic discrimination are highly individual, and both policy as well as interpersonal factors contribute to the outcome of potentially discriminating events. |
| Wagner et al. (2016), USA (30) | to investigate patient perspectives and experience with ALS genetic testing. | Quantitative study, survey (n= 449). | ALS, genetic testing | The results indicate that ALS patients may have limited access to genetic testing, but perceive benefit from this service. |

**Table 3: Summary of the included studies (n=24)**

Table 3. The Data analysis process

| **Authentic expression, meaning units underlined** | **Subcategories** | **Subcategories** | **Main category** |
|---|---|---|---|
| Motivations for testing included *preparing for the future*, *making decisions* (e.g., insurance, career romantic relationships, and childbearing), and *relieving the feeling of uncertainty* (20) | The motivations to undergo genetic testing | ***Individuals' emotional aspects*** | **Decision-making in genetic testing as a dilemma: balance between autonomy and responsibility** |
| Major reasons included *freedom from living with ambiguity*; *reduction of anxiety*; *desire to make appropriate lifestyle decisions*, including taking preventive measures (17) | | | |
| Justifications not to pursue testing at the current time included *not wanting the result to limit one's future*, *feeling unsure how one would respond to results*, *recognizing that one's genetic status was not going to change*, and *being too scared to know whether HD would manifest in their future* (20) | The main reasons for not pursuing genetic testing | | |
| The main reasons for not pursuing predictive testing were: (i*) there is no treatment for HD* (*n* = 10/15,66.7%) and (ii) *concern about it causing psychological harm, like anxiety and depression* (*n* = 10/15,66.7%). (24) | | | |
| A key factor for participants was to do the right thing for their children (29) | To obtain genetic information for other family members at risk of having hereditary disease | ***Responsibility towards others*** | |
| Other motivations included o*btaining information for other family members* (n = 3), *solidarity with other family members who previously asked for testing* (n = 2), *pressure from the spouse* (n = 1) and financial investment (n = 1) (22) | | | |
| These young people expressed concern *about the impact of their test result on other members of the family both relatives and partners*. Indeed several described their *desire to avoid causing pain to family members who may have been affected themselves and/or watched the devastating effects of the condition. (23).* | Fear of harming others by providing them genetic information | | |
| These young people expressed concern about the impact of their test result on other members of the family both relatives and partners. Indeed several described their *desire to avoid causing pain to family members who may have been affected themselves and/or watched the devastating effects of the condition.* (20) | | | |

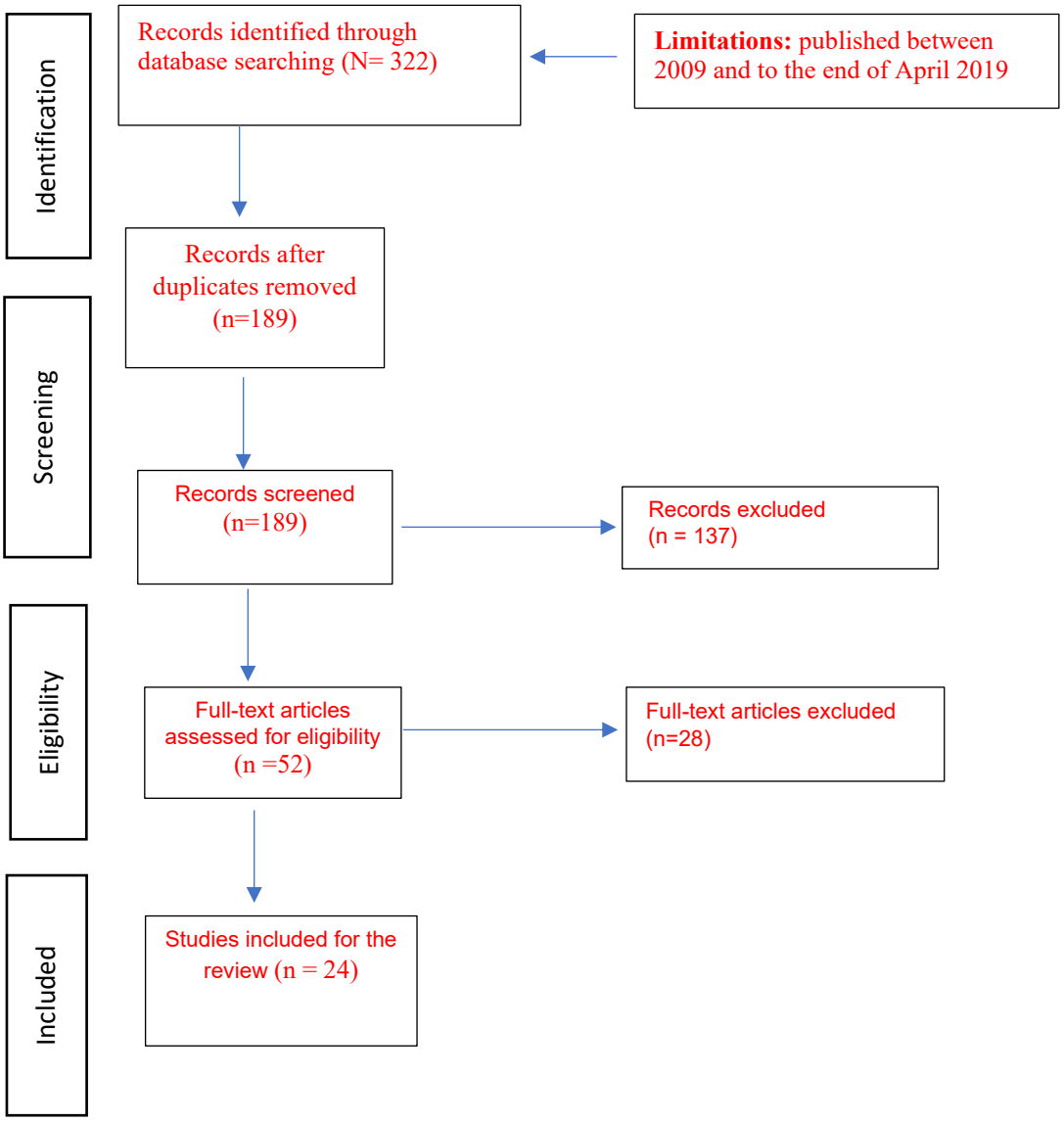


Figure 1. PRISMA flow diagram of study selection process

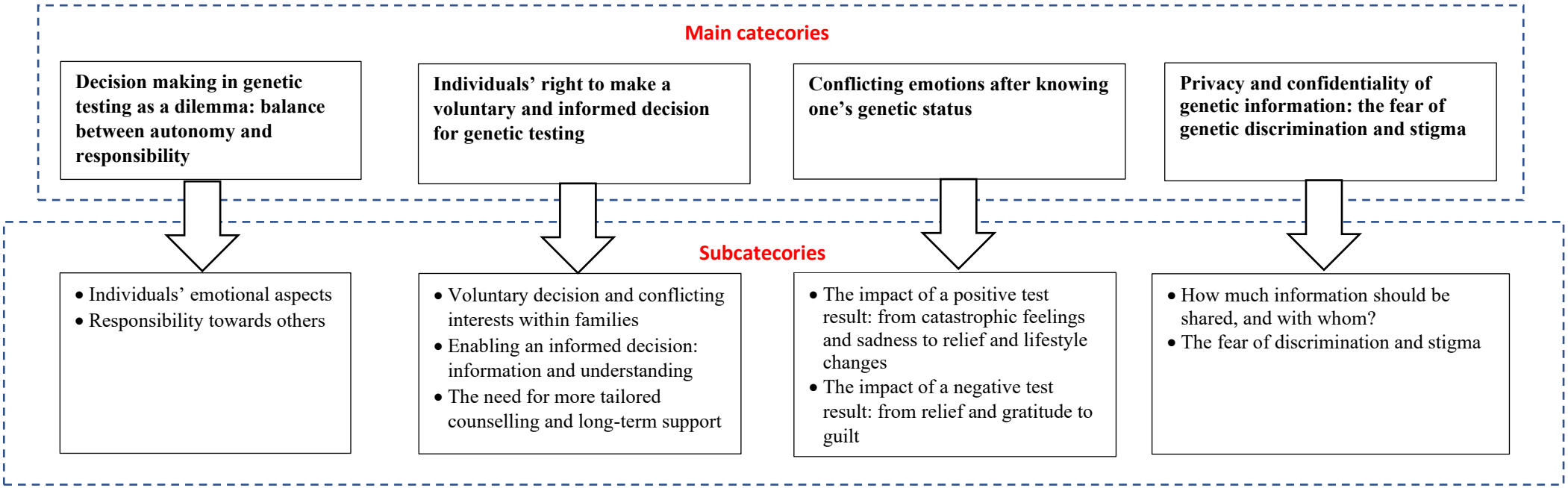


**Figure 2: The ethical implications of genetic testing in neurogenerative diseases**