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GECONEU

GENETIC COUNSELING IN EUROPEAN UNIVERSITIES: THE CASE OF NEURODEGENERATIVE DISEASES

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TRANSNATIONAL IMPLEMENTATION GUIDELINES FOR GENETIC COUNSELING IN NEURODEGENERATIVE DISEASES

The GECONEU Consortium consists of:

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HUEI	Network Aging Research, Heidelberg University	Germany
Fundacio ACE	Fundacio Ace Alzheimer Center Barcelona	Spain
VUB	Vrije Universiteit Brussel	Brussel
IEU	Izmir Ekonomi Universitesi	Turkey
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1. INTRODUCTION

1.1. Introduction to this Guide

1.1.1. What's the scope of this Guide?

This Guide is part of the GECONEU project which focuses on developing a Course on Genetic Counseling (GC) on Neurodegenerative Disorders (ND). This project's main goal and central impact is to support people and society to understand better the aims of Genetic Tests (GT) and the usefulness of GC by involving students in an innovative learning and teaching setting. This project will provide the opportunity to consider all the factors of an appropriate training course for society by involving the families of people with ND in developing the learning and teaching outcomes, consequently improving visibility and enhancing the level of knowledge. More information about the project can be found on the website: http://www.genecounsel.eu/.

The main aim of this Guide is to provide basic information about the GT in ND as well as practical guidelines on how to implement GC in ND. It can be used as a protocol that includes specific steps for conducting GC in ND. With guidelines, we refer to, in addition to official guidelines, written statements, recommendations, and reports that address issues related to GC. It will be part of the GECONEU Course.

It is crucial to highlight that this Guide cannot replace the extended Guides focusing on GC in practice. This Guide is just an overview of other best practices and summarizes the main results.

1.1.2. How was this guide developed?

This Guide is the result of some research on the GECONEU project consortium. Partners of this project come from the Network Aging Research of the Heidelberg University, Aristotle University of Thessaloniki, Vrije Universiteit Brussel, Izmir Ekonomi Universitesi, Fundació Ace. Institut Català De Neurociències Aplicades and Panhellenic Institute of Neurodegenerative Disorders. They worked as a team in order to search for existing GC protocols and recommendations in European countries. They also shared the questionnaire ''Perceptions regarding pRE-symptomatic Alzheimer's Disease Screening'' (PRE-ADS) to families and relatives to collect the needs of families on GC and GT. The perspectives of experts and professionals in the field were investigated by quantitative research with five focus groups, which focused on the ideal GC and qualifications of healthcare professionals to be genetic counselors and the training characteristics of GC.
This Guide combines the above research underlying potential ethical issues that come to the surface on the GC and GT process.

1.1.3. Who is this guide for?

These guidelines can be used by clinicians who implement GC to families of people with ND. As it is part of the GECONEU Course which focuses on an introduction to GC, it can also be used by participants in the Course like students of Health and Life science as well as Biomedical

Departments like biology, medicine, nursing, sociology and psychology, etc. or other professionals in the field of Health Sciences who are interested in learning more about GC. It is crucial to highlight that the implementation of GC depends on national law, and in some countries, GC may only be done by specialized persons like human geneticists.

1.1.4. How to use this guide?

This Guide includes a first part with a short theoretical section of the main types of GT that exist as well as the informative values for these tests. It provides a short description of the central ND and their genetics and the prerequisites for predictive GT and GC. It continues with definitions of GC and recommendations and existing GC protocols. We highlight the ethical issues regarding GT and GC of ND. In the second part, the Guidelines for implementing GC in ND are presented. The main tools that can be used in GC and the crucial issues that need to be paid attention to by a genetic counselor are also included in the last part.

• 1.2. Introduction to genetic testing

1.2.1. Introduction

A GT examines a person's genetic material. This can help, for example, to assess the risk of a disease or to detect hereditary diseases. A blood sample or a small amount of saliva is usually used for the examination. So far, genetic tests have only been helpful for a few diseases. Because the results of a genetic test can also affect children and siblings, they may only be performed under certain circumstances.

On one hand, this is regulated by the "General Data Protection Regulation" (GDPR, https://gdpr-info.eu/), which applies to all EU member states. Some countries also have national laws, such as the Gene Diagnostics Act in Germany (Bundesamt für Justiz 2010). The aim of the Genetic Diagnostics Act (GenDG) and its guidelines is to

> **"Determine the conditions for GT and to prevent discrimination based on genetic characteristics, in particular, to uphold the state's obligation to respect and protect human dignity and the right to informational self- determination"**
> **(§ 1 GenDG)**

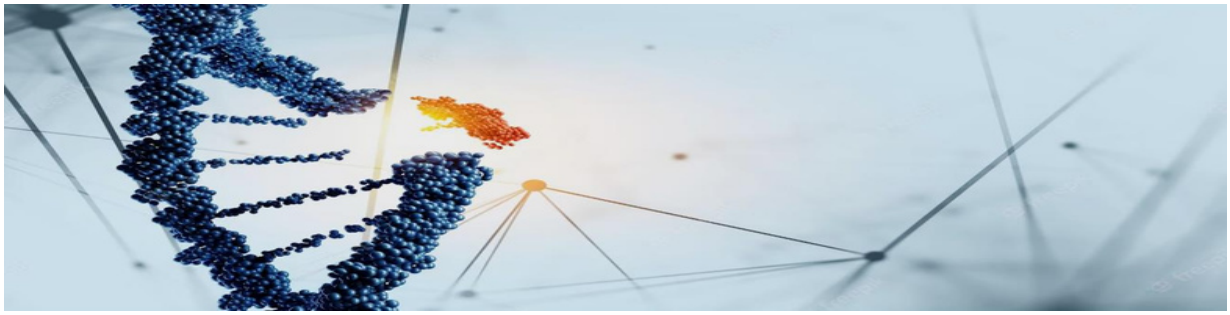
1.2.2. What types of genetic tests do exist?

Depending on the significance of the result, three different types of GTs can be distinguished:

- **Diagnostic genetic tests:** Their main task is to find the cause of an already existing disease.
- **Predictive genetic tests:** They are used to identify certain peculiarities in a person's metabolism that, for example, influences the effect of a drug or that, together with environmental influences, can trigger a disease. Predictive genetic tests can help plan treatment.

- Prognostic genetic tests: They can be used to estimate the risk of future diseases. They can also provide information about how likely it is that a genetic trait or disease will be passed on to one's children.

These tests are also used in law enforcement or to clarify parentage, such as in a paternity test.



1.2.3. Informative value of genetic tests

Since the results of genetic tests are sensitive data on one hand and represent "family data" on the other, they can lead to serious individual, family and psychosocial problems and influence reproductive decisions. However, it is crucial to understand that the validity of some genetic tests is low. Therefore, education and GC are of particular importance. This must be tailored to the needs of the person seeking counseling and help in the decision-making process for or against GT. Therefore, it is necessary to provide basic medical-genetic knowledge that enables the person to make a self-determined decision. In this context, it is particularly important that those seeking advice are able to classify the relevance of the results for their further life and have sufficient time to think about decision alternatives (knowledge – right not to know). The right not to know provides that is widely recognised by several international and national biomedical instruments and knows. Therefore, there are several laws that establish this right. Listed below are some of them, adapted from Andorno 2013.

The right not to know in international biomedical instruments Article 5.c. of the Human Genome and Human Rights (1997) states, “The right of every individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected”. Article 10 of the International Declaration on Human Genetic Data (2003) declares, “When human genetic data (...) are collected for medical and scientific research purposes, the information provided at the time of consent should indicate that the person concerned has the right to decide whether or not to be informed of the results. This does not apply to research on data irretrievably unlinked to identifiable persons (...). Where appropriate, the right not to be informed should be extended to identify relatives who may be affected by the results”. Article 10.2 of the European Convention on Human Rights and Biomedicine (1997) says, “Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed”.

Article 7.d. of the Declaration on the Rights of the Patient (Lisbon Declaration) states that "the patient has the right not to be informed on his/her explicit request unless required for the protection of another person's life".

The World Health Organization (WHO) Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services (1997) provides that "the wish of individuals and families not to know genetic information, including test results, should be respected, except in testing of newborn babies or children for treatable conditions".

The right not to know in several national laws Article 7.3 of the Belgian Law on Patients' Rights (2002) states, "The information will not be provided to the patient if he or she expressly so requests, unless the non-disclosure of this information causes a serious harm to the patient or a third party, and provided that the physician has previously consulted another professional practitioner about this and heard the opinion of the patient's trustee".

Article 9.1 of the Spanish Law on Patient's Autonomy (2002) provides that "When patients explicitly express their wish not to be informed, such a wish must be respected". Article 11.4 of the German Law on Genetic Diagnosis (2009) provides that "The results of a genetic test should not be disclosed to the concerned persons if they have decided (...) that they should be destroyed, or if they have withdrawn their consent to the test" (Deutscher Bundestag 2009).

The regulations of the right not to know thus respect the own wish of the person to be counseled and his or her family to decide against the communication of the results. In general, the explicit wish and the decision of the person and his or her family are prerequisites for GT. Therefore, GC must be non-directive and in a generally understandable form as well as open-ended.

1.2.4. Genetics and genetic tests for neurodegenerative diseases

ND leads to progressive loss of brain function and overlapping clinical syndromes. For example, cognitive deficits occur not only in Alzheimer's disease (AD) but also in frontotemporal lobar degeneration dementia (FTLD), AD with a cerebrovascular component, and dementia with Lewy bodies (LBD). Similarly, the motor system is affected in amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), and spinocerebellar ataxias (SCA). Common to all diseases is that symptoms (with few exceptions) do not appear until adulthood, making age the most important risk factor (Gan et al. 2018).

GT are now available for a number of hereditary diseases. However, the extent to which this is informative for the individual depends primarily on the type of inheritance.

The most common test that is performed is the one for HD. The GT is usually carried out as part of family planning, i.e., when one of the parents of the couple wishing to have a child has HD and the risk should be ruled out that one has inherited the gene oneself – even if the disease has not yet broken out – and it should be prevented that one's own children could get the gene.

Alzheimer's disease (AD) is the most common cause of neurodegenerative dementias, accounting for 60-70% (WHO 2023). A distinction is made between AD with late symptom onset after age 65 and early-onset AD before age 65. While the early-onset forms may be due to monogenic, highly penetrant mutations in the APP, PSEN1, and PSEN2 genes, the late-onset form of AD often occurs sporadically. Its occurrence is determined by a complex interaction between genetic and epigenetic factors as well as environmental and lifestyle factors. Although APOE ε4 is the strongest genetic risk factor for AD, the effect of APOE ε4 accounts for only 27.3% of the estimated heritability of 58-79% (Bajaj et al. 2018; DGPPN 2017).

Frontotemporal lobar degeneration dementia (FTLD) is a clinically and pathologically heterogeneous group of non-Alzheimer dementias characterized by selective, progressive cortical atrophy involving the frontal or temporal lobes. FTLD is much less common than AD. The population prevalence is estimated at 4-5 per 100,000 before age 65. The age of onset is typically in the sixth decade of life. However, it may begin as early as the early 30s or as late as the ninth decade. Approximately 20-50% of FTLD patients have an affected first-degree relative. FTLD has a significant genetic component with an autosomal dominant or X-linked inheritance.
It is estimated that 10% of patients with FTLD have a disease caused by a mutation in a single gene. To date, many gene variant mutations have been discovered, but there are four common high-risk gene variants that contribute to inheriting FTLD: MAPT, GRN, and C9orf72, and TBK1. Those, as well as other mutations, are listed in the AD and FTLD mutation database (http://www.molgen.vib-ua.be/FTDMutations) (DGPPN 2017; Goldman and van Deerlin 2018; Pottier et al. 2016).

Huntington's disease (HD) (Huntington's chorea) is a rare, steadily progressive, debilitating, and ultimately fatal ND of the central nervous system. The disease causes gradual destruction of cells in specific areas of the brain. This causes the gradual deterioration of physical, mental, and psychological functions. As a result, the main symptomatology is choreatic movements, dementia, psychiatric symptoms like psychosis, depression, or behavioral symptoms. The current prevalence is circa 5 per 100,000. Huntington's disease is caused by a pathological expansion of the CAG repeat in the huntingtin gene (HTT) on chromosome 4. The normal length of the CAG repeat range is between 10 and 35, with low penetrance between 36 and 39 repeats, while patients with 40 or more repeats are most likely to express the disease. The longer the CAG repeat range, the earlier the disease onset (Medina et al. 2022; Trostdorf et al. 2014). Huntington's disease is a genetic disorder that is inherited in an autosomal dominant manner. Children of parents in which one parent carries the affected gene have a 50% chance of inheriting this gene and developing the disease. Concerning family planning, the risks should be weighed carefully. In GT, the detection of more than 38 of the CAG repeat is considered pathological (Trostdorf et al. 2014).

Amyotrophic lateral sclerosis (ALS) is a progressive ND characterized by selective loss of motor neurons in the motor cortex, brainstem, and spinal cord. The dysfunction and loss of these neurons lead to muscle weakness, atrophy, and eventual paralysis of the limb, bulbar, and respiratory muscles. The prevalence of ALS is 1-9 per 100,000, and most ALS occurs in individuals without a family history. The average onset age in clinical trials and population studies is between 58 to 64 years, but the disease can affect people of any age. Familial ALS starts on average about 5 years earlier.

Familial ALS is most commonly inherited in an autosomal dominant disorder. Less commonly, it can be inherited in an autosomal recessive or X-linked manner. Mutation of the gene SOD1 can be present in both familial (20%) and sporadic ALS (10%) (Checkoway et al. 2011; Ghasemi and Zahediasl 2012; Mehta et al. 2019).

Parkinson's disease (PD) is the second most common ND after AD. The prevalence can reach 2% in individuals over 65 years of age (Checkoway et al. 2011). Diagnosis is based on clinical findings of tremor, rigidity, and bradykinesia. Psychiatric manifestations such as depression and visual hallucinations are common but not uniformly present. Dementia eventually occurs in at least 20% of cases, and 80% of all PDs are considered sporadic (idiopathic) with symptom onset after age 60.

Non-Mendelian PD is thought to be due to the effects of multiple genes as well as environmental risk factors (Litvan et al. 2007; NCER-PD 2019). Mendelian (monogenic) forms of PD occur in less than 5% of all patients and are inherited autosomal-dominantly, autosomal-recessively, or very rarely X-linked. Mendelian forms of PD have an earlier age of onset than families with typical late-onset PD. The clinical picture is similar to sporadic forms of Parkinson's in most cases. Alterations in gene loci (genes in parentheses) PARK1/PARK 4 (SNCA/α-synuclein gene), PARK8 (LRRK2), PARK17 (VPS35) are dominant forms, in PARK2 (PRKN), PARK6 (PINK1), PARK7 (DJ-1) are considered recessive. Mutations in some of these genes may also play a role in cases that appear to be sporadic (not inherited). Mutations in the GBA gene increase the disease risk but do not cause disease in all carriers (Hopfner and Höglinger 2020; Mielke C and Krüger K 2013; NCER-PD 2019).

1.2.5. Prerequisites for predictive genetic testing and genetic counseling

The current practice of GT and counseling for each ND is described in the medical guidelines of the medical committees. For each ND, the requirements for predictive GT are distinct and may also differ from country to country. Therefore, depending on the disease and which country you are in, you should consider in ND both the medical guidelines and the national guidelines for GT. Here is an example from the German guideline on PD issued by the German Society of Neurology (DGN), which includes a chapter on GT:

The prerequisite for GC and testing is that (i) at least two first-degree relatives have PD, or if (ii) disease manifestation occurs before the age of 45 (DGN Deutsche Gesellschaft für Neurologie 2016, p. 28)

In Germany, GT of monogenic forms of PD is currently performed primarily to confirm diagnosis in younger patients or for the benefit of professional and personal life planning. According to the Gene Diagnostics Act, GC before and after diagnosis is mandatory for predictive GT. If a monogenic etiology is suspected, testing of corresponding genes can be considered (DGN DeutscheGesellschaft für Neurologie 2016; Mielke C and Krüger K 2013).

Table 1. Main characteristics of the most common neurodegenerative diseases

Diagnosis	Prevalence	Possible onset	Characteristics	Genetics
Late-onset Alzheimer's disease	60-70% of all diagnosed dementias; 30% of people aged 85 and older	> 65	progressive symptoms including cognitive, behavioral, neurological, and systemic symptoms, functional deficits (activities of daily living)	Sporadic interaction of genetic factors (major gene APOE ε4 27.3%) and environmental factors (58-79%)
Early-onset Alzheimer's disease	1-5% of all Alzheimer's disease cases	< 65 years	Variety of symptoms including cognitive, behavioral, neurological, and systemic symptoms	Monogenic high-penetrance mutations in the APP, PSEN1, and PSEN2 genes
Frontotemporal lobar degeneration (FTLD)	10% of all dementias; 4-5 per 100.000	< 65 years	Progressive, cortical atrophy in frontal or temporal lobes Changes of personality and behavior, disturbances language and cognition	major component with autosomal-dominant or X-linked inheritance; four major genes MAPT, GRN, C9orf72 and TBK1 mutations
Huntington's disease	5 per 100.000	> 40 years	choreatic movements, dementia and psychiatric symptoms	Monogenic autosomal dominant; pathologically increased CAG-repeats (>38) in the huntingtin gene HTT
Amyotrophic lateral sclerosis (ALS)	1-9 pro 100.000	> 60 years	Selective loss of motor neurons in the motor cortex, brainstem and spinal cord; muscle weakness, atrophy, paralysis of the limb, bulbar and respiratory muscles	Sporadic interaction of genetic factors (mutation of the SOD1 gene in 10% of cases) and environmental factors
Familial amyotrophic lateral sclerosis (ALS)	10% of all ALS cases	≈ 5 years younger than sporadic ALS	Selective loss of motor neurons in the motor cortex, brainstem and spinal cord; muscle weakness, atrophy, paralysis of the limb, bulbar and respiratory muscles	Mostly autosomal dominant, more rarely autosomal recessive or x-linked;Mutation of the SOD1 gene in 20% of casesC9orf72 mutations

Morbus Parkinson (idiopathic)	>80% of all Parkinson's diseases; 2% of people aged 65	> 65 years	Tremor, rigidity and bradykinesia. Partial Psychiatric manifestations such as depression and visual hallucinations.	Sporadic interaction of genetic factors and environmental factors
Familial Parkinson's disease	5-10% of all Parkinson's diseases	> 65 years	Tremor, rigidity and bradykinesia. Partial Psychiatric manifestations such as depression and visual hallucinations.	Autosomal-dominant inheritable genes α-Synuclein, LRRK2, VPS35 (gene loci PARK1/PARK 4, PARK8, PARK17);recessively inheritable genes PRKN, PINK1, DJ-1 (gene loci PARK2, PARK6, PARK7);GBA gene is a genetic risk factor

1.2.6. Investigations in embryos, children and adolescents

In Germany, the Genetic Diagnostics Act (Art. 15.2) stipulates that prenatal GT aimed at determining genetic characteristics of the embryo or fetus for a disease that, according to the generally recognised state of medical science and technology, does not develop until after the child reaches the age of 18 may not be performed.

GT in children and adolescents may be performed only if it is necessary to determine the cause of the disease or to clarify the differential diagnosis of existing symptomatology and only if effective medical measures can be taken to prevent the disease itself or to prevent complications or to treat it. In the case of diseases that become manifest in childhood or adolescence and for which no therapeutic or preventive measures are available at the time of the genetic diagnosis sought, the benefits and risks of predictive diagnostics must be carefully weighed in the context of GC. The reasons for performing an examination must be all the more urgent the more serious the diagnosis or disease in question. An examination may be considered if it is deemed valid to avert the psychological or social impairment of the child. In contrast, predictive diagnostics may not generally be performed in healthy children and adolescents for a disease that does not occur until adulthood (Microsoft Word – 2013_08_01_Stellungnahme Kinder und Jugendliche.doc (gfhev.de)) (Deutscher Bundestag 2009).

• 1.3. Introduction to genetic counseling

1.3.1. What is genetic counseling?

According to the National Society of Genetic Counselors (2006) and the EuroGentest Network of Excellence, GC is a communication process that deals with the occurrence, or risk of occurrence, of a (possibly) genetic disorder in the family and helps people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.

The process helps the individual or the family to
(1) understand the **medical facts** of the disorder;
(2) appreciate how **heredity contributes to the disorder** and the risk of recurrence in specified relatives;
(3) understand the **options for dealing with the risk** of recurrence;
(4) use this genetic information in a personally meaningful way that **promotes health, minimizes psychological distress and increases personal control;**
(5) choose the **course of action** which seems appropriate to them in the view of their risk and their family goals, and act in accordance with that decision;
(6) make the best possible **adjustment to the disorder** in an affected family member and/or to the risk of recurrence of that disorder.

1.3.2. Recommendations and existing genetic counseling protocols

According to the Recommendations for GC related to GT of the EuroGentest Network of Excellence (www.eurogentest.org), most European Countries do not have national legal provisions on GC. Here are the references of the specifications at the international level and the guidelines from Germany as an example.

Table 2. Recommendations at the international level and guidelines from Germany

	EuroGentest Network of Excellence – Recommendations for GC related to GT https://sfmg.se/download/externadokument/publikationer/guidelines_of_GC_final.pdf European Society of Human Genetics-ESHG or ESHG endorsed Documents https://www.eshg.org/eshgdocs European Board of Medical Genetics - Proposes a Code of practice for GC as well as revises the core competencies of counselors and members of a GC team. https://www.ebmg.eu/897.0.html
Germany	Guideline of the Genetic Diagnostics Commission (GEKO) on the requirements for the qualification for and content of GC pursuant to Section 23 Para. 2 No. 2a and Section 23 Para. 2 No. 3 GenDG https://www.rki.de/DE/Content/Kommissionen/GendiagnostikKommission/Richtlinien/RL-GenetischeBeratung.html Factual Report – GC in Germany – Structure and Utilization – GenBln 2 https://www.rki.de/DE/Content/Kommissionen/GendiagnostikKommission/GenBIn2/Bericht_GenBIn2.pdf?__blob=publicationFile

According to international guidelines and policies, the most critical issues related to genetic counseling are the following:

(1) Appropriate training for the counselors
(2) Content of the information
(3) Counselors' understanding of the information
(4) Psychological support
(5) Problems related to disclosure to the relatives
(6) Need for consent
(7) Autonomy
(8) Confidentiality
(9) Fear of discrimination

The next section analyzes the most important ethical issues regarding GT and GC.

1.3.3. Ethical issues regarding genetic testing and genetic counseling of neurodegenerative diseases

Regardless of the type of GT (predictive, diagnostic, or prognostic), in most, if not all, European countries, one session of GC is required prior to testing and one prior to notification of inheritance. GT are not only used in medicine. In Germany (Richtlinie der Gendiagnostik-Kommission 2011), but also in Switzerland (SAKK) and Austria (Satzinger 2006), GT may not be offered without appropriate counseling. The purpose of counseling is to provide the patient with the basic knowledge necessary to make an autonomous decision in the first place.
In medical ethics, the four ethical principles proposed by (Beauchamp and Childress 2019) apply above all: autonomy, beneficence, non-maleficence, and justice.

Autonomy: Beauchamp and Childress' definition of autonomous decision-making includes the conditions of intentionality, understanding, and non-control. Although Beauchamp and Childress acknowledge that social influences are unavoidable and permissible to some degree, their approach to autonomy has often been criticized as being too individualistic, since the influence of social relationships on human decisions cannot be ignored. An alternative concept is that of relational autonomy, which incorporates social relationships and their influence on decisions and actions (Zimmermann et al., 2021). Empirical studies have confirmed that family considerations often influence GT decision-making (Etchegary et al. 2010). Particularly in the case of predictive GT that reveals individuals based on information about relatives, one question is the extent to which relatives should have a say in whether such a test is performed and whether the results may, should, or even must ultimately be shared with relatives. However, since everyone has a right "not to know," i.e., a right not to know genetic risk information (Andorno 2004), this leads to potential dilemmas when individuals from the same family have different preferences (Zimmermann et al. 2021).

Beneficence: Careful consideration should be given to whether the expected results are expected to provide a benefit to the person seeking testing or to the future child/generations. A benefit would be expected if the results of GT can prevent the onset of the disease, treat it or at least slow down its progress. On the other hand, testing is problematic when there is a test but no cure (yet), as in the case of testing for APOE ε4 for late-onset AD.

Non-Maleficence: It is required that the GT does not cause any harm. Since only a blood or saliva sample is required for a GT, no physical harm is to be expected, but the test can trigger anxiety. It should, therefore, be carefully weighed up to what extent the expected result represents a benefit for the person or whether the burden of the test is to be rated higher.

Justice: Under equity, primarily distributive justice is to be considered, i.e., to what extent GT is accessible to all people – regardless of socioeconomic status and the country where the person lives. In addition, the results may contribute to injustice and especially to discrimination and stigma, for example, if the results are provided to health insurers or employers. Therefore, the prohibition of discrimination must be observed, which has already been established since 1997 in Article 2a of UNESCO's "Universal Declaration on the Human Genome and Human Rights": "Everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics'' (UNESCO 1997).

2. Genetic Counseling Implementation Guidelines on Neurodegenerative disorders

2.1. Introduction

The preparation of these GC guidelines has been based on the review of the following protocols and research programs which are considered pioneer programs in their field:

- PICOGEN program - a GC intervention for dementia in Spain (Fortea et al. 2011)
- The Italian protocol "Italian Dominantly Inherited Alzheimer's and Frontotemporal Network -IT-DIAfN" (Bocchetta et al. 2016)
- The research protocol of 20 years program REVEAL (Risk Evaluation and Education for Alzheimer's Disease) by the Harvard Medical School (Green et al. 2009; Roberts et al. 2012)
- The "Joint practice guidelines of the American College of Medical Genetics and the National Society of genetic counselors" (Goldman et al. 2011b)
- The "Gold standard for Genetic Testing for adults onset conditions" by the Huntington Disease Society of America's Guidelines for GT for Huntington's Disease (Migliore et al. 2019)
- The Genetic Counseling Intervention of Dominant Inherited Alzheimer's Network (DIAN) of Washington University (Aschenbrenner et al. 2020)
- The protocol of the research program Alzheimer Prevention Initiative (API) (Langlois et al. 2019)
- The "Process of Genetic Counseling" document developed by the Human Genetics Society of Australasia in 2012

The GECONEU project team has written these guidelines according to a literature review and the project's main results of Project Result 1 (PR1). The main aim is to assist genetic counselors and other healthcare professionals involved in the GT process for ND and to protect the well-being of individuals who choose to be tested. The guidelines are a framework of recommended procedures for testing; they are not regulations. Each provider, center, or institution that offers GT for ND and each testing situation is unique. Providers must ensure that testing is performed safely despite patient, personnel, and geography variations, patient, personnel, and geography variations.

Persons involved in the GC process

According to Rantanen et al. (2008), the main persons who are involved in the GC process are described in Table 3 (Rantanen et al. 2008).

Table 3. Main persons who are involved in the GC

Counselor	
Profession	Person who gives GC should be a professional specialist, as he needs to convey complex information. Local providers of GC and disclosure must be qualified per local laws and regulations governing GC and associated licensure requirements of providers. In areas where no regulations exist, it is recommended

	that providers of GC and disclosure be trained clinical professionals with an advanced understanding of genetics and experience with providing potentially sensitive medical results.
Training	Genetic counselors should receive appropriate and ongoing training in genetic conditions, risk assessment, psychosocial issues, bioethics, service system, communication and patient perspective. Guidelines for the training of clinical geneticists and genetic counselors can be found on the following websites: https://www.nsgc.org/; www.hgsa.org.au; https://www.ebmg.eu/. It is also acknowledged that different clinical genetics units and/or services may function differently and are administered by various public and private health facilities.
	Co-operation within The GC team consists of a team of professionals. Particularly complex *the healthcare system* genetic conditions require a multidisciplinary focus. It comprises physicians, geneticists, social science researchers, health educators, legal experts, and genetic counselors, medical ethics, and disclosure of genetic risk factors.
Family	
Asymptomatic people	A protocol based on specific steps for implementing GC is recommended, e.g. International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines.
Symptomatic people	GC for symptomatic people should be performed in the presence of the individual's legal guardian or family member.
Vulnerable people / Not able to consent	Tests should be done in the best interest of the people that cannot give informed consent, or sometimes in the health interest of their family. Authorization of the representative is required, but the persons must participate according to their capacity.

2.2. Steps for implementing genetic counseling in neurodegenerative disorders

It is essential to highlight that there are differences in the counseling process according to each disease. Here, we recommend the basic steps for GC in ND, which need to be adapted by the professional in each case.

This protocol includes five components comprising the GC disclosure process, whose core features include the pre-consultation contact, the preparation of the consultation, the main steps and structured content of counseling, the GT and disclosure session in-clinic ssessment

of a well-being, the assessment of psychological readiness for disclosure and evaluation of disclosure impact.

Step 1. Pre-consultation contact

The genetic counselor should contact the client before the scheduled clinic appointment in writing, face to face, or by phone in order to:

• confirm consultation details like the place, day, time, etc.

• outline and explain the purpose, the process and the aims of the consultation, including the possibility of a physical examination so that concerns that the client may have regarding the nature and conduct of the consultation may be addressed

• clarify unrealistic expectations of the clinical consultation

• ascertain the needs and expectations of the client/family (their agenda), identifying any special requirements, e.g. wheelchair access or interpreter services. Social and/or cultural issues which may impinge on the consultation may be identified by the counselor

• identify necessary documentation, such as post-mortem reports, pathology results, and names of attending specialists and hospitals where treatment was received

• provide emotional support to reduce any pre-clinic anxiety

In some cases, the genetic counselor can give or send an informative brochure, which can be used as self-directed learning materials and covering content typically addressed in a pretesting GC session. They can include information about the process and aims of the consultation, a summary of the genetic condition, mutations, risk genes and their relationship to each inherited disorder, considerations for learning one's gene genotype for both the participant and their family, e.g. potential emotional responses, implications of ND risk for blood relatives. There is an example of American brochures in Annex 3.

Step 2. Preparation for consultation

✓ check that all information needed for the consultation has been obtained

✓ review relevant health unit records and/or clinical genetics unit records

✓ discuss the case with the supervisor or with relevant colleagues as necessary

✓ review relevant medical literature

✓ prepare and set the agenda. The agenda must consider the needs and expectations of the client or family. It is essential for the counselor not to proceed with her / his own agenda without establishing the individual's, couple's or family's needs and perceptions. It needs to include educational information that will be given to the client, like the specific disease, the available relevant genetic tests, including appropriate support group information and fact sheets as applicable

✓ prepare for any personal questions/concerns that the individual will express

Step 3. The consultation

Consent form

Signed consent forms need to be obtained from the client or other relatives. It is generally accepted that informed consent is necessary before conducting any session and tests on individuals. Informed consent ensures that individuals thoroughly understand the purpose, benefits, risks, and limitations of the counseling and testing process and can make a voluntary decision about whether or not to proceed.

The client should be informed about the possible uses of their information including their right to access their own information and that their information may be given to another medical practitioner in the course of their management (if relevant) only after consent is given to do so. The client should also be informed that their information and family history information may be stored on a statewide database, password-protected and only accessed by trained genetic health professionals.

For children or individuals who are not able to provide informed consent, the responsibility falls on their parents or legal representatives to provide authorisation for GT. This ensures that decisions about testing are made in the best interest of the individual, considering their health and well- being.

Psychological and Cognitive Readiness Assessment

Genetic information often has a profound impact on an individual and their family. This should be acknowledged in the counseling process and clients must be given a safe environment in which to express their emotional /psychological responses. As well as dealing with genetic issues, counselors should offer emotional support to clients during the consultation and/or in follow-up contact sessions. To reduce the risk of adverse psychological reactions to disclosure of genetic results, measures to assess psychological readiness to receive results must be administered. The most well-known measures of mood and cognition with established clinically meaningful defined score range for screening for psychological readiness are included in Table 4.

In this step, a presentation can also be prepared by the counselor to facilitate the procedure (an example https://alzheimerspreventioninitiative.com/wp-content/uploads/2020/12/Generation-1_Standardized_APOE_Handout_V5_Public.pdf).

Table 4. Main scales for assessing psychological status and cognitive functions.

Symptoms	Psychological and Cognitive scales	Links/resources
Depression	15-item Geriatric Depression Scale (GDS)	https://integrationacademy.ahrq.gov/sites/default/files/2020-07/Update_Geriatric_Depression_Scale-15.pdf
	21-item Beck Depression Inventory (BDI)	https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Personality-&-Biopsychosocial/Beck-Depression-Inventory/p/100000159.html
	Hamilton Depression Rating Scale (HAM-D)	https://dcf.psychiatry.ufl.edu/resources/measurement-resources/
	20-item Center for Epidemiological Studies-Depression Scale (CES-D)	https://pubmed.ncbi.nlm.nih.gov/9189988/
Anxiety	21-item Beck Anxiety Inventory (BAI)	https://www.pearsonclinical.co.uk/store/ukassessments/en/Store/Professional-Assessments/Personality-&-Biopsychosocial/Brief/Beck-Anxiety-Inventory/p/P100009033.html
	Hamilton Anxiety Rating Scale (HAM-A)	https://dcf.psychiatry.ufl.edu/resources/measurement-resources/
	Six-Item Subset of the State-Trait Anxiety Inventory for Adults (STAI-AD)	https://bpspsychub.onlinelibrary.wiley.com/doi/10.1111/j.2044-8260.1992.tb00997.x
Suicidal ideation and behaviors	Columbia Suicide Severity Rating Scale (C-SSRS)	https://cssrs.columbia.edu/training/training-options/
Cognitive impairment	Montreal Cognitive Assessment (MoCA)	https://mocacognition.com/

Motives and considerations

Beginning GC by inquiring about the patient's experience with the disease, values and beliefs, and personal and family needs allows the counselor to assess the patient's understanding of the disease as well as any misperceptions and to learn their responses to experiencing the disease in their family member(s) and their fears about the future. The genetic counselor can then use this information to explore feelings about being part of a family with this disease and living at risk for the disease and how the patient has managed to live with the threat of the condition.

The counselor may emphazise significant variation in how each person with this disease experiences the disease course. The counselor can facilitate a client's understanding that if she or he tests positive for this disease, her or his personal experience may differ from that of their family member because of the variability of clinical symptoms, personality, support, environment, or new treatments. GC integrates this information into the discourse about the patient's experiences. Often, misperceptions are expressed.

Before helping the patient anticipate the possible ramifications of testing, learning about the patient's motivation for pursuing predictive testing at this point may illuminate the context into which the information will be received and who is available to help support the patient. The counselor may ask the patient to consider their responses to the following questions:

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

The genetic counselor may recommend delaying testing until unresolved issues between a couple are addressed and/or may refer them for longer-term counseling (Goldman 2020).

Considerations for symptomatic patients

Because GT of a symptomatic individual is typically requested by a relative concerned about his risk, the counselor must remain alert to any potential conflicts of interest, such as lack of interest of the symptomatic patient or other at-risk family members. If the symptomatic patient is inclined to be averse to testing, it is not recommended. Instead, DNA banking should be explored. If there is disagreement within the family regarding whether testing should be performed, a family meeting is strongly encouraged (with or without the genetic counselor present). A family meeting would allow all interested parties to discuss the potential impact of the GT on the family, how test results will be communicated, and how to respect the rights of those family members who do not wish to know the results.

Finally, it is important for the genetic counselor to check the client's level of understanding throughout the consultation and present all the potential options, in order to enable the client to make an autonomous and informed decision:

• all available options need to be presented without bias
• the advantages and disadvantages of each option need to be discussed within the context of individual values and beliefs
• the client's reaction to each option and consequences should be explored
• the client needs to understand that they are in control of their own decisions
• the counselor should ensure that clients are given sufficient time to deliberate and seek further relevant input as necessary

Review personal medical and family history

Information may be gathered in several ways. Information about the client/family medical history may be available via the referring doctor and hospital/medical records. Results of previous tests and other investigations may also be accessible via the referring doctor, hospital/medical records, or directly from the laboratory. The genetic counselor must be aware of the confidential nature of medical information and always obtain consent from the client before accessing this information.
Counselors are entitled to record a family medical history if it is necessary for **the care of the client.**

The construction of a **family pedigree** is an integral part of the GC process and as family information can be highly sensitive, great care needs to be taken to maintain confidentiality.

In the recording of the family history, the genetic counselor needs to begin with a short introduction about why this information is being collected and an explanation of how it will be used, who will have access to it, and how it will be archived. At collecting information, the counselors need to start the questions to the individual himself, and if any: his/her partner, children and pregnancies. They have recorded details of each person's name, age, physical and mental condition, and the number of children, children's parents, children's parents and children's parents' health or, in cases of death, the age and cause. Any health problems, such as the ND, the age of onset of symptoms, the pathological conditions, and any medical conditions findings, current ages, or ages at death (mainly unaffected relatives), and causes of death need to be assessed in detail. It is essential to remember that some family members may have different pathological features while having the same disease. It shall be clarified whether all children are with the same partner, whether they all have the same biological parents, and whether there are cases of adoption.
Then, all relevant information about the person's siblings and all about their children are recorded. Counselors continue collecting information relating to the father and mother of the person and continue with the brothers and sisters of the father and mother and all other blood relatives until a complete family tree is established. A ≥3-generation family history should be obtained. The history of additional relatives may prove helpful, especially in small families or those with a preponderance of early death that may mask a history of dementia (Goldman et al. 2011a).

For the design of the family pedigree there detailed rules are used and internationally accepted symbols. For those who wish to learn more about the methods of designing pedigrees, more information can be found in Bennett et al. (2008) “Genetic Counseling”. Also, there is a variety of software with different capabilities, complexity and cost, such as "Cyrillic" or "Progeny". An example of a pedigree is presented in Figure 1.
It should be underlined that a family pedigree is a way of recording family history and is therefore designed simultaneously with the taking of the family history.

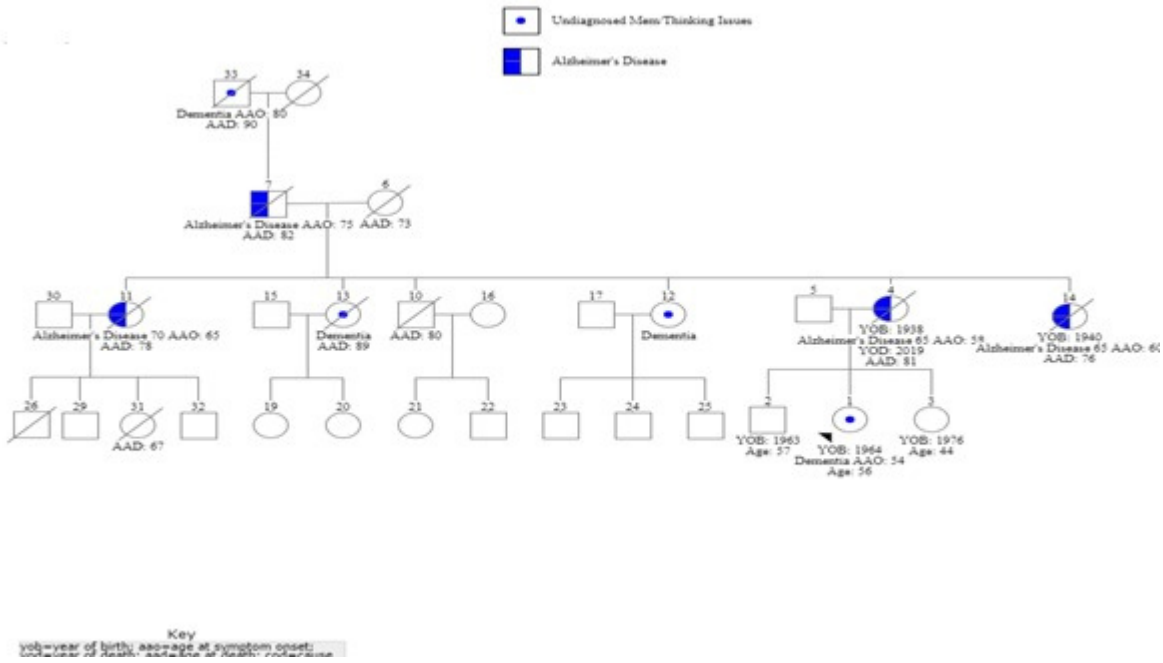
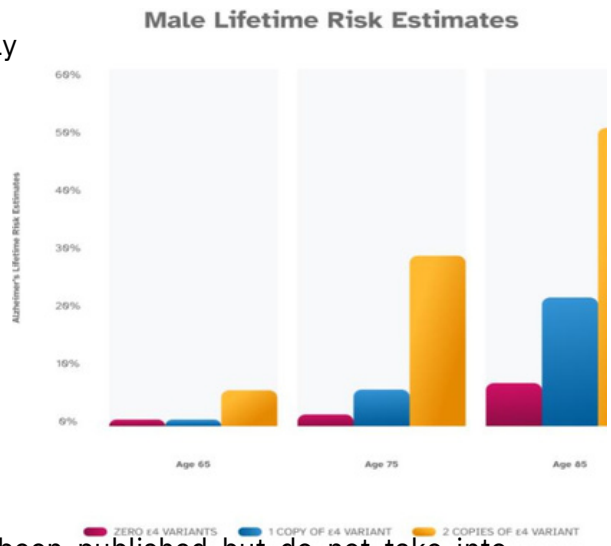


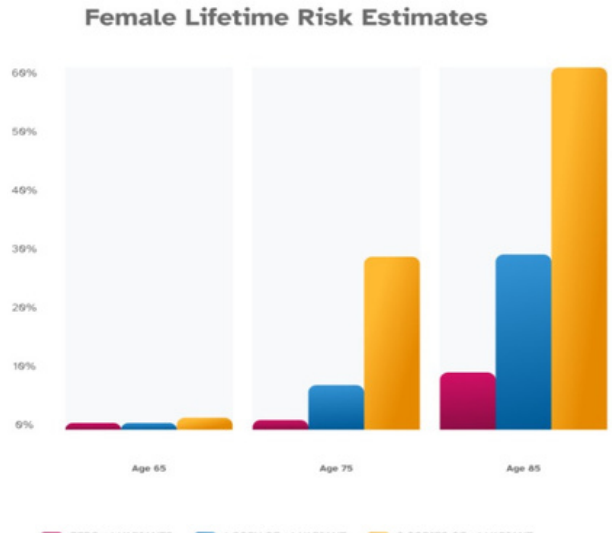
Figure 1. An example of a pedigree with an Alzheimer's disease history

Estimation of the risk



Once a diagnosis is made in a family or there is a family history, individual risk can be estimated using empirical data, inheritance patterns, pedigree information, clinical expertise and test results. The counselor should counsel the client about risk interpretation and the limitations of risk calculations. The risk associated with the most genes and mutations not only varies widely between studies but also is often reported as an odds ratio, which is difficult to translate into meaningful figures for individual counseling. For instance, cumulative risk curves for first-degree relatives of patients with AD stratified by APOE genotype and gender have been published but do not take into consideration multiple first- and second-degree relatives affected with AD and are based only on population studies of individuals of European or African American descent (Goldman et al. 2011b).

Green et al. (2009), in the REVEAL study, created risk curves for the disclosure process that were specific for age and sex, showing the lifetime cumulative incidence of AD and the remaining risk of AD for each subject (cumulative incidence from current age to the age of 85 years). These curves are available in the Supplementary materials



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2778270/ #SD1.

Also, as part of the API GC and Disclosure Process, lifetime risk estimates in the corresponding APOE GC and disclosure materials were developed to help guide participants through the APOE disclosure sessions. These included an educational handout summarizing considerations for undergoing disclosure APOE, handouts used by providers of disclosure to walk participants through the APOE disclosure sessions, and results summary sheets for each possible APOE genotype. PDF versions of these materials can be downloaded by clicking the links on this website https://alzheimerspreventioninitiative.com/

The detailed information on how to estimate the risk is out of the scope of this document.

Further information can be found in the book “Introduction to Risk Calculation in Genetic Counseling” developed by Young (2007). Step 3. Genetic tests

The main GT for ND:

Genetic screening

Screening tests are used to determine one’s risk for having a particular disease. These tests are performed on people who do not show any signs or symptoms of said disease (https://medlineplus.gov/genetics/). This risk assessment is always compared to the risk of the general population. In case of an increased risk (i.e., a positive result), there is an above-average risk of developing the disease. One has to keep in mind that these types of assessments result in estimates, which means that there is a possibility of false positives (i.e., the test shows a positive result, but the person is unaffected) or false negatives (i.e., the test shows negative results but the person is affected).

Furthermore, the result of these tests does not guarantee said outcome, e.g., a positive test result does not guarantee that this person will develop the disease. It only describes that this person has an above-average risk of developing said disease. They can help guide the next steps, such as deciding whether additional diagnostic testing is needed.

An example of such a test is noninvasive prenatal testing (NIPT), where the fetus' risk for genetic abnormalities, such as Down syndrome, is tested.

Diagnostic testing

Genetic diagnostic tests are used to test for a certain suspected diagnosis based on the presented symptoms and signs (https://medlineplus.gov/genetics/). These tests can either confirm or rule out a diagnosis. Furthermore, they can give insight into the chance of developing or further passing on said disease. A diagnostic test can be performed at any life cycle stage, but is not available for all genes or genetic conditions. The results of a diagnostic test can heavily influence a person's choice about healthcare and disease management.

Predictive and presymptomatic testing

Predictive and presymptomatic testing detect genetic mutations associated with diseases that often appear at older age, such as neurodegenerative diseases (https://medlineplus.gov/genetics/). These tests are useful for those who have affected family members but do not present symptoms or signs of that disease (yet). While predictive testing can identify a genetic mutation that increases a person's risk of developing a certain disorder (i.e., risk genes), presymptomatic testing can find out whether or not a person will develop a certain inheritable disorder before the first symptoms or signs are visible (i.e., deterministic genes). Similar to diagnostic tests, results from predictive or presymptomatic tests can help a person's decision on medical care.

Susceptibility testing

Susceptibility testing is a type of genetic testing that uses methods, such as polygenic risk scores (PRS), to estimate the relative genetic susceptibility of someone, based on their genetic profile, to develop a certain disease (Manrique de Lara et al. 2019). PRS is a powerful tool that can successfully identify persons at-risk and estimate their risk for developing a certain disease by also considering the effects of genome-wide common variants that are uncovered through GWAS. However, the results are difficult to interpret for diseases, such as neurodegenerative diseases, because of their complexity and other non-genetic factors that may influence the development of the disease (e.g., modifiable risk factors). It is important to remember that susceptibility testing is mostly probabilistic and mainly used for research purposes, as their accuracy is not yet sufficient for routine clinical practice.

An example of susceptibility testing is testing for the APOE gene in people who have family members with a diagnosis of AD, whereas an example of presymptomatic testing is testing for PSEN1 in those who have family members diagnosed with AD at an early age.

Pharmacogenetic testing

Pharmacogenetic testing is not the same as genetic testing but rather a type of precision medicine. It uses genetic information to determine how you will respond to certain medicines and treatments (https://medlineplus.gov/genetics/). Based on this information, your healthcare provider can assess what medicine and dosage is needed for optimal treatment. The tests can use a sample of saliva, blood or cells swabbed from your cheek and the results will give you an overview of gene variants that show how a certain medicine will likely affect you. However, these results cannot diagnose or disclose what risk you may pose for developing a certain disease.

Carrier testing

Carrier testing is used to see whether someone "carries" a genetic variation (allele) associated with a certain disease or trait (https://www.genome.gov/genetics-glossary/Carrier-Screening). One

speaks of a carrier when that person has a normal and a variant allele, one from each parent. This type of testing is mainly performed to search for inheritable diseases passed on recessively when the person thought to be a carrier does not show symptoms of said disease.

Step 4. Disclosure session

Before disclosure of genetic results and associated risk estimates, the counselor must confirm the participants' continued desire to learn their results. In the disclosure session, the genetic counselor announces the results and discusses the following points:

● inheritance implications, degree of risk comparisons, and potential risk modifiers

● a Risk Estimate Summary Sheet corresponding with the participant's genetic result is given to the participant at the end of the session

● revisit the individual's plans regarding with whom and how the results will be shared

● assist the client and participating family members with informed decision making

● discussion on treatment or management options and the availability and status of the disease research and/or DNA banking

● referral to a more appropriate expert treating professional may be required (facilitated via liaison with the referring medical practitioner), as most genetic consultations provide a clinical geneticist's opinion or diagnosis, or are for education and counseling support and rarely involve ongoing management or treatment

● provide resources for more information. There is currently no cure for most ND, and because of this, some people decide not to discover their genetic risk. Other people will choose to be tested because of medication, treatments or participation in clinical trials may be used to delay or ease symptoms, and there are also lifestyle changes that address some ND risk factors. These lifestyle changes can include diet, intellectual activities, exercise, heart health, decreased anxiety and depression, and increased social interaction and good communication with others. Many resources underlie these changes, like

- National Institute on Aging: www.nia.nih.gov/health
- Institute of Medicine: www.iom.edu/cognitiveaging

The genetic counselors can offer resources for more information (brochure with prevention strategies). Clients need to consult with a healthcare professional before making any significant lifestyle changes.

Step 5. Follow-up sessions

Client follow-up is an essential component of the GC process to assess the impact of participants learning their genetic results. This ascertains that the client understands the information, allows further questions to be addressed and provides further support to the client. The health professional is responsible for offering re-contact from the client after a clinic appointment to address any additional concerns. Some genetic specialist clinics are involved in treating and managing clients and providing long-term follow-up.

You can complete the post-disclosure follow-up with the participant by telephone or in person. Specific batteries assess the impact of the disclosure administered 2-7 days, 6 weeks, 6 months, and 12 months after disclosure. Assessments include measures of participant psychological well-being, understanding and retention of the information presented throughout the GC and

disclosure process, perceptions of perceived risk and threat of ND, and assessments of the general impact of testing and motivation for learning these results, as well as participant satisfaction with the genetic services provided. Apart from the scales that are referred to Table 4 and measure psychological impact, some additional scales that are used in the follow-up sessions in order to evaluate the impact are the following:

- Impact of Event Scale (IES)
- Impact of GT for Alzheimer's disease instrument (IGT-AD distress)
- Genetic Counseling Outcome Scale (GCOS-24)
- Genetic Counseling Satisfaction Scale (GCSS)
- Behavioral changes are measured using self-reported questionnaires (1) changes in diet, (2) changes in exercise, or (3) changes in medications and/or vitamins
- Risk recall with open-ended response items, participants are asked to recall the lifetime risk estimates they were provided

2.3. Main materials and tools that can be used

1) Pre-disclosure genetic education materials

In the condensed model that can be completed in a single visit, many counselors develop self-directed learning materials like educational pre-disclosure videos and disclosure informational brochures. These are sent to participants before the GC and disclosure visit and cover content typically addressed in a pretesting GC session. They usually provide a summary of the specific gene and its relationship to the disease, as well as considerations for learning one's genotype for both the participant and their family (e.g., potential emotional responses, implications of the disease risk for blood relatives). The video can incorporate several multiple-choice questions with feedback explaining the correct response to help confirm and reinforce participant understanding. Participants are strongly encouraged to review these materials in advance of the counseling and disclosure session to orient and familiarize themselves with the information addressed during the session. These key points are also included in the study of informed consent forms to ensure participants are presented with this information before enrolling in the trial.
An example of a brochure can be found here https://www.coe.int/t/dg3/healthbioethic/Activities/07_Human_genetics_en/Brochure/en_geneticTests_bd.pdf. This brochure was created by the Council of Europe with the title "Genetic Tests for Health Purposes". An example of a video can be found herehttps://www.genedx.com/patients-families/education

2) Genetic Counseling and disclosure session materials

Several supportive materials are used in the GC and disclosure sessions to help standardize the process. In Alzheimer Prevention Initiative (API) (Langlois et al., 2019), a Genetic Counseling and Disclosure Session Handout and a set of Genetic Counseling and ~~Disclosure Session~~ Talking Points ~~(Table 5) have been developed to help standardize the content of the session~~. The counselor uses the handout as a visual aid during the sessions and participants are provided with a copy for note- taking and to keep. APOE Risk Estimate Summary Sheets are available for each possible genotype in this handbook and are provided to participants after the session to serve as a record of their

results and the associated risk information reviewed during the session. This handout can be found on the website of API https://alzheimerspreventioninitiative.com/wp-content/uploads/2020/12/Generation-1_Standardized_APOE_Handout_V5_Public.pdf
The counselor uses the "Talking Points" as a reference guide for the session. These points highlight key topics to be addressed during the session but are not intended to be exhaustive or restrictive.

Table 5. Genetic Counseling and Disclosure Session Talking Points GC and disclosure session talking points with individuals receiving first-time disclosure of their APOE results

1. Introduction to session
2. Review the purpose of the session and confirm the individual's interest in participation
3. Review family history, with a focus on AD/dementia
4. Basic clinical description of AD, Mild Cognitive Impairment, and dementia
5. Impact of APOE on AD risk
a. Cannot definitively predict or rule out the development of AD
b. No medical management is currently available based on APOE status
c. Review three possible results and associated AD/Mild Cognitive Impairment risk
i. Zero copies (ε3/ε3, ε2/3, ε2/ε2)
ii. One copy (ε3/ε4, ε2/ε4)
iii. Two copies (ε4/ε4)
6. Inheritance of APOE; address possible implications for children and siblings
7 Considerations for learning APOE results
a. Psychological impact
b. Familial impact
c. Clinical research impact
8. Review potential Genetic Information Nondiscrimination Acts (different in each country, this pertains to the United States only)
9. Address specific concerns or considerations about learning APOE result
10. State option to either proceed with disclosure of APOE GT results, postpone disclosure to a later date, or decline disclosure of APOE results in
a. If proceeding with disclosure, talking points 11–15 would follow
b. If postponing, review the plan for the participant to recontact the site when ready to proceed with disclosure. Address remaining questions and concerns before ending the session
c. If declining disclosure, participants would be given time to address their questions or concerns before ending the session
11. Disclosure of APOE results
12. Disclosure of AD risk information
a. Provide comparison for other APOE genotypes to provide context
13. Allow participants to ask questions and/or discuss issues of concern or interest that are of most importance to them after learning the result
14. Address the participant's emotional response to the result (if any)
15. Review the plan for follow-up phone calls by the counselor

3) Record keeping

Clinical genetics units should have client files separate from records of the health unit to which they are attached. This is recommended because of the:
• confidential nature of genetic information
• need to maintain the record for future generations
• need to have a complete and comprehensive file for each family
• need to have access at central clinical genetics units to the records of clients seen in outreach areas

The information to be documented and retained includes:
• genetics file number as appropriate
• identifying information - name, date of birth, address, phone number
• date and place of consultation
• names of health professionals and other individuals present at consultation
• name of referring health professional and other health professionals involved in their care
• reason for referral
• client history, test results and reports from other health professionals / hospitals
• pedigree – minimum three generations
• diagnosis and documentation to confirm as appropriate
• relevant information about members of the extended family
• summary of information given to client and the counseling issues addressed
• agreed process for providing client with results of investigations as appropriate
• copies of consent forms for accessing medical records, DNA testing or sample storage
• copies of correspondence to client and health professionals
• arrangements for follow up

4) Communication techniques in disclosure

Ideally, knowledgeable healthcare professionals experienced in communicating sensitive health risk information should divulge results, with telephone and videoconferencing as acceptable alternatives to in-person disclosure. Given widely varying levels of health literacy and numeracy among laypersons, communication may need to be tailored to individuals receiving risk information. Thus, communication and counseling skills are some of the critical skills that a counselor has to cultivate to effectively influence change in a client, like genuine interest in others, self-reflection, ability to listen, accessibility and authenticity, etc. More information on how to cultivate these skills can be found in the book of Leroy et al "Genetic Counseling Practice: Advanced Concepts and Skills" (Leroy 2021).

5) Provide guidance on appropriate next steps

Genetic disclosure should be accompanied by recommendations for reducing disease risk. Although there are no proven means of preventing most ND, several health behaviors and interventions show promise in lowering the risk of the disease, including regular physical activity and management of hypertension. The WHO summarized such approaches in its recently issued guidelines for risk reduction. Individuals should also be made aware of substantive education resources such as the Alzheimer's Association and the US National Institute on Aging. In addition, encouragement to participate in clinical research may sometimes be appropriate. All key information disclosed to individuals should be concisely summarized in a take-home document for future reference.

2.4. Important issues that need to be paid attention

Apart from the ethical issues and recommendations that are referred to the above sections (1.2.3 and 1.3.3), a genetic counselor needs to be pay attention to the following issues:

The right not-to-know. Pre-test counseling includes discussion about the rights to know and to decide, including the right not-to-know.

Discrimination. Genetic information, if given to other family members or outside agencies such as insurers or employers, has the potential to result in discrimination and stigmatization, so this issue should be discussed during the consultation.

Common information. Genetic information is common to the whole family, which can cause conflicts. Counseling should be available to at-risk relatives. It should be considered before the test how they are contacted. Patients have a duty to contact their at-risk relatives, but this should not be a condition for test, as sometimes they have good reasons not to. Disclosure should be agreed between the client and the physician.

Cultural issues. When providing information, the family's cultural and ethnic background should be taken into account.

GT is different. Genetic information differs from other health information because it has familial and generational implications, it is predictive, and the emphasis is not on treatment. It is severe, private and complex and deals with special ethical dilemmas.

Referrals. Referrals can be made to other professionals when necessary. Reason for a referral can be, e.g. support, treatment or ethical reasons.

Periods. There should be enough time between counseling and decision-making. The waiting time should, however not be too long, at least the test results should be disclosed as soon as possible. Patients should be informed about the time between the appointments.

Venue. A GC session often involves personal and sensitive issues. The venue chosen needs to ensure privacy, quiet, absence of distractions, as much privacy as possible and be comfortable.

Receipt of referral / Intake. This will usually be a referral letter or phone call from the person referred or from the referring health professional. Written referrals are preferred as this facilitates continuity of care following the consultation.

Finally, **the most common questions that could be asked** to a genetic counselor are the following: • Does this disease run in my family?
• If my family member has this disease, might I get it? If yes, should I get tested?
• If I have this disease, are my family members at risk to get it?
• Is GT available for this disease? If yes, what are the benefits and limitations of testing? How will I pay for it?

- What kind of information could GT for this disease give me?
- What does the GT process involve?
- How could knowing more about genetic risk help me?
- Could I be exposing myself or my family to discrimination based on genetic information?
- Could GT results affect my health care coverage?

3.1. Consent form

An example of an Informed Consent can be found in the Supplementary materials of the publication (Green et al. 2009) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2778270/ #SD1

3.2. Other tools for GC process

Some examples of materials can be found in the following links

PRESENTATIONS

https://alzheimerspreventioninitiative.com/wp-content/uploads/2020/12/Generation-1_Standardized_APOE_Handout_V5_Public.pdf

LEAFLETS

https://memory.ucsf.edu/sites/memory.ucsf.edu/files/wysiwyg/UCSF_Patient%20Eduation_Genetic%20Counseling_v5_11-6-17%20.pdf

https://memory.ucsf.edu/sites/memory.ucsf.edu/files/wysiwyg/UCSF_Provider_FamilyHealthHistory_11-6-17.pdf

https://memory.ucsf.edu/sites/memory.ucsf.edu/files/wysiwyg/UCSF_Provider%20Eduation_Genetic%20Counseling.pdf

https://memory.ucsf.edu/sites/memory.ucsf.edu/files/wysiwyg/UCSF_Provider_GeneticResultsInterpretation_11-6-17.pdf

Supplementary materials of (Roberts et al. 2012)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3718049/

3.3. Definition of abbreviations

Abbreviations	Definition
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
API	Alzheimer Prevention Initiative
DGN	German Society of Neurology
EU	European Union
FTLD	Frontotemporal lobar degeneration dementia
GC	Genetic Counseling
GDPR	General Data Protection Regulation
GenDG	Genetic Diagnostics Act
GT	Genetic Test
HD	Huntington's disease
LBD	Lewy bodies dementia
ND	Neurodegenerative Disorders
PD	Parkinson's disease
PR	Project Result
REVEAL	Risk Evaluation and Education for Alzheimer's Disease
SCA	Spinocerebellar ataxias
WHO	World Health Organization

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