Diagnosis, Genetic Counseling and Risk Assessment in Alzheimer's Disease: Methodologies, Implications, and Ethical Considerations

Paula Denisa Saragea

Alexandru Ioan Cuza" University of Iași

Abstract:

Introduction: Alzheimer's disease (AD) is a complex neurodegenerative disorder with significant genetic and environmental components. Accurate diagnosis, genetic counseling, and risk assessment are essential for managing the disease and informing preventive and therapeutic strategies.

Materials and Methods: The study conducted included a comprehensive review of current diagnostic criteria for AD, including the NINCDS-ADRDA, DSM-V-TR, and Romanian guidelines. The study examined methodologies for genetic counseling and risk assessment, focusing on both early-onset (EOAD) and late-onset (LOAD) forms of AD. The analysis integrated data from clinical evaluations, neuroimaging, genetic testing, and empirical risk tables to assess recurrence risks and provide guidance for genetic counseling.

Results and Discussion: Diagnostic criteria for AD require the presence of cognitive deficits, progressive neurodegenerative processes, and exclusion of other conditions. Genetic counseling involves assessing family history, calculating recurrence risks based on empirical data table, and considering both mendelian and non-mendelian inheritance patterns. Genetic risk factors, such as mutations in PSEN2, APP, PSEN1, and APOE ε4, significantly influence the likelihood of developing AD. The recurrence risk is categorized into low, moderate, high, and very high levels, depending on genetic findings and familial patterns. The counseling process must be personalized, taking into account the patient's educational level, psychological state, and ethical considerations.

Conclusion: Accurate diagnosis and effective genetic counseling are crucial for managing AD and informing at-risk individuals. Understanding genetic risk and recurrence probabilities aids in personalized prevention strategies and decision-making. Genetic counselors play a vital role in providing tailored advice while adhering to ethical standards and ensuring informed, empathetic communication with patients and their families.

Keywords: dementia, Alzheimer's disease, management, genetics, neurodegenerative, multifactorial disorders, diagnosis, genetic counseling, risk assessment, recurrence risk, methodology, ethical considerations

Introduction

Memories, for human beings—ephemeral in the grand scheme of the universe, fleeting moments that gent-

ly pass through the gateway of existence marked by the only certainty, death—are, as the writer and philosopher Mircea Eliade described, icons of the past. They remain the sole portals through which significant moments, marked by intense emotions in each individual's life, can be vividly recalled and relived, allowing the evocation of long-forgotten fragments. The irreversible passage of time, a silent witness to the writing of the pages and chapters in the novel of a being's existence, naturally leads to the onset of aging (senescence) processes, subtly giving rise to the moment when the human being, weakened and with diminished physiological functions, shapes their life around memories, recalling the past. However, the natural course of life's stages is often abruptly interrupted at different points by the onset of neurodegenerative processes, which inevitably lead to the development of a broad spectrum of clinical, heterogeneous pathologies, including Alzheimer's disease (AD), specifically affecting the neurons of functional anatomical structures and neural circuits.

Progressive or chronic dementia, a clinical condition with multiple underlying causes, is defined as a syndrome involving the continuous deterioration of cognitive and motor functions, cerebral atrophy, neurotrophic depletion, and overall cognitive and non-cognitive decline. This syndrome results in severe disability, total dependence in the advanced stages, and ultimately, premature death. Dementia is predominantly attributed to AD, responsible for 50-70% of cases. This neurodegenerative disorder begins subtly and progresses in a continuous and irreversible manner, with periods of functional, cognitive, and behavioral decline punctuated by intermittent phases of stability (plateaus). Typically, AD is a multifactorial condition, shaped by a variety of influencing factors. The second leading cause of dementia is of vascular origin, accounting for approximately 17-29% of cases. Additionally, the mixed form of the two previously mentioned conditions (AD and vascular dementia), leads to neurodegeneration in approximately 10-23% of cases. [1–3]

Research on the heritability of AD reveals that genetic factors account for approximately 60-70% to 80% of the risk, while environmental factors contribute only about 20-40% to the overall risk profile. Similar genetic contributions are observed in other conditions such as schizophrenia, an endogenous psychosis, and asthma, a chronic respiratory condition, where genetic factors also account for roughly 80% of the risk. In cardiovascular diseases, such as hypertension and coronary artery disease, genetic factors account for around 60% of the risk. Moreover, insulin-dependent diabetes mellitus shows a genetic contribution of about 70% to its risk determination. [3–5]

Multifactorial diseases, characterized by their complex etiologies, exhibit a global prevalence of approximately 50-70 per 1,000 in the adult population. Between 5% and 10% of these conditions fall into this category of combined determinants, which are understood at a molecular level through mechanisms that can be categorized into two distinct groups:

- The Oligogenic Hypothesis describes how specific, rare (low-frequency) allelic variants of certain genes contribute to a limited degree of genetic predisposition, susceptibility, or vulnerability. These variants typically have a minimal qualitative effect on the overall genetic risk.

- The Polygenic Hypothesis suggests that genetic predisposition is triggered by a combination of environmental factors and numerous small-effect allelic variants across multiple genes. These variants collectively contribute to a cumulative genetic risk, each variant having a modest quantitative impact. [6–10]
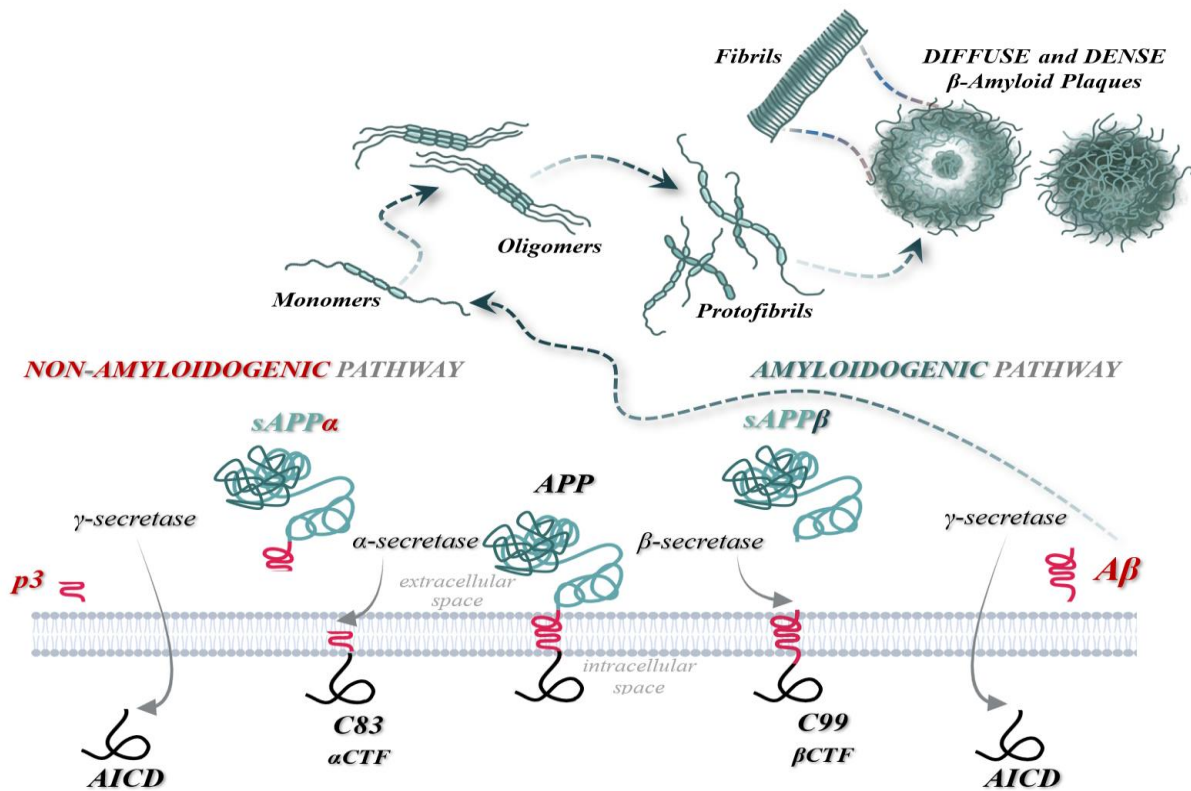
Figure 1. The processing of Amyloid Precursor Protein (APP) via Two Distinct Pathways: "Non-Amyloidogenic Pathway" and "Amyloidogenic Pathway"

AD has a broad etiology, being complex, multifactorial, and polygenic. It can be driven by the accumulation of extracellular insoluble β-amyloid plaques (also known as senile or neuritic plaques)(Figure 1), acute-phase inflammatory responses, NFTs (intracellular neurofibrillary tangles of hyperphosphorylated TAU proteins)(Figure 2), and imbalances in neurotransmitters such as dopamine, serotonin, or norepinephrine. Genetic factors also play a role, including mutations on chromosomes 1, 14, 19, and 21. Additionally, mitochondrial dysfunction(Figure 2), exposure to harmful toxic substances (such as aluminium, pesticides, and organic chemicals), certain infectious agents like herpes, metabolic disturbances, and associated conditions such as traumatic brain injuries (TBI), diabetes, hypertension, and obesity can contribute to the onset of neurodegenerative processes. The development of cerebrovascular amyloidosis and a deficit of acetylcholine and acetylcholinesterase, known as the cholinergic hypothesis, as well as the proliferation of apolipoprotein E4, can further contribute to the onset of AD. [3]
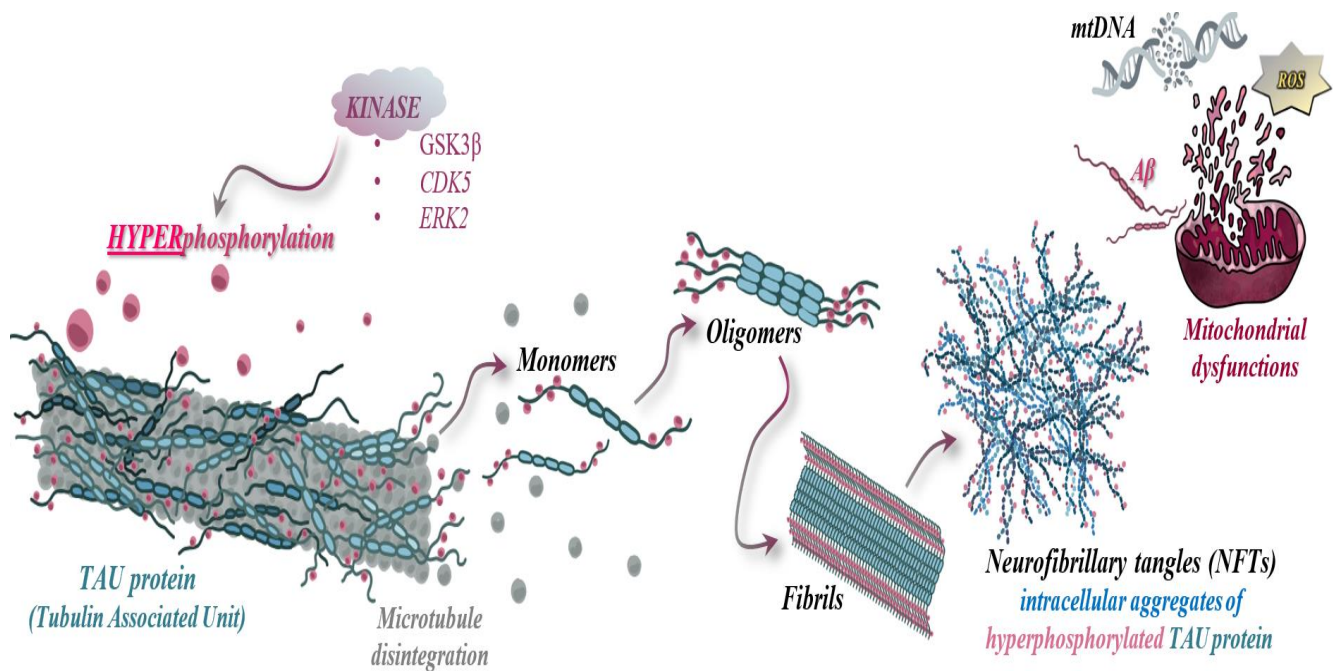
Figure 2. The pathogenesis of AD: NFTs, Oxidative Stress, mtDNA degradation, and Mitochondrial Dysfunction

Materials and Methods

The study employed a comprehensive methodology that included several key components:

- Literature Review: An extensive review of the literature was conducted, focusing on academic books from university library collections, as well as a variety of peer-reviewed articles, including review articles, meta-analyses, original research, and clinical studies. This review aimed to capture the current knowledge on diagnostic methodologies and genetic counseling in AD.

- Medical Records Analysis: The research involved an in-depth analysis of medical records, including additional investigation results and diagnostic data. This component sought to evaluate the real-world application and effectiveness of diagnostic and genetic counseling methods.

- Examinations and Cognitive Assessments: Data were collected from cognitive assessments, general clinical exams, neurological evaluations, psychiatric evaluations, and neuropsychological tests. This comprehensive approach was designed to identify prevalent diagnostic practices and provide insights into the methodologies used in both clinical and research settings.

- Information Extraction: The study extracted relevant information from these various sources to analyze and synthesize current practices in diagnostic methodologies and genetic counseling for AD.

The goal of the study was to identify and evaluate existing methodologies for diagnosing AD and providing genetic counseling, to enhance understanding and improve practices in these areas.

Results and Discussion - Literature Review
Classification

Under the broad category of the clinically heterogeneous syndrome referred to as "dementia," which is characterized by a range of symptoms including global cognitive decline (such as aphasia, apraxia, agnosia, impairment in executive functions like abstraction, organization, planning, and sequencing,

difficulties in recalling previously known information, and challenges in encoding and storing new concepts), there exists a diverse array of chronic neurological conditions that impact the central nervous system (CNS) of patients at various stages of the disease. To ensure accurate identification and differentiation of Alzheimer's disease—the most common form of dementia—multidisciplinary teams consisting of diagnostic experts (including geneticists, neurologists, psychologists, psychiatrists, and geriatricians) are assembled to perform differential diagnoses. [11,12]

Thus, AD must be identified through the exclusion of other possible pathologies. Dementias are classified both evolutionarily and etiologically according to the "National Guideline for Diagnosis and Treatment of Dementia", published by the Ministry of Health of Romania, into three categories:

- **progressive, continuous, and irreversible dementias** [e.g., late-onset AD (LOAD), early-onset AD (EOAD), dementia resulting from Parkinson's disease, mixed dementias (AD with Parkinson's disease, cerebrovascular disease, vascular or Lewy Bodies dementia), frontotemporal dementia (FTD), Creutzfeldt-Jakob disease (CJD), Huntington's disease, multiple sclerosis, HIV/AIDS-related dementia, vascular dementias, multi-infarct or post-stroke dementia, neurosyphilis]

- **non-progressive and irreversible dementias** [e.g., post-anoxic or post-traumatic dementia]

- **reversible dementias of other etiologies** [e.g., neoplastic dementia, Wilson's disease - associated with familial hepatolenticular degeneration, subdural hematoma-induced dementia, chronic hypoglycemia, liver, chronic renal failure, and dialysis dementias, which are metabolic-related neurodegenerations, toxic dementias (chronic alcoholism, carbon monoxide poisoning, pesticide or heavy metal exposure (Mn, Hg, Pb, Au, As, Bi), cocaine use, Li and Al exposure), medication-induced dementias (tricyclic antidepressants, anxiolytics, antipsychotics, sedatives, digitalis, trihexyphenidyl, barbiturates), endocrine-related dementias (hypothyroidism, hypopituitarism, Cushing's syndrome), nutritional deficiency dementias (Folate, vitamin B12 deficiency associated with subacute combined degeneration, vitamin B1 deficiency - Wernicke-Korsakoff syndrome, vitamin B3 deficiency – Pellagra), autoimmune-related dementias such as SLE (systemic lupus erythematosus) and vasculitis, and infection-related dementias (meningitis, parasitic infections, neuroborreliosis, tuberculosis, encephalitis, HIV/AIDS, chronic meningoencephalitis: cryptococcosis, meningovascular syphilis)]

Based on the data obtained from additional clinical and paraclinical evaluations, the diagnostic orientation can be guided by the diagnostic criteria, which categorize dementias as follows according to the guidelines published by the American Academy of Neurology and the European Federation of Neurological Societies:

- **dementia without neurological or clinical manifestations specific to other pathologies**: AD, FTD, HIV/AIDS-related dementia, dementias caused by unspecified degenerative diseases

- **dementia associated with other pathologies, characterized by the presence of specific clinical or laboratory signs**: chronic intoxication, prolonged hypoxia, hypoglycemia, extended exposure to heavy metals or pesticides, paraneoplastic limbic encephalitis, chronic meningoencephalitis, nutritional deficiencies, endocrine disorders, AIDS/HIV, acquired or familial hepato-lenticular degeneration.

- **dementia not associated with other pathologies, characterized by neurological signs invariably associated with**: Myoclonic epilepsy, lipidosis, Huntington's disease, Strausler-Scheinker syndrome (prion-type myoclonic dementia), Parkinson's disease, CJD, Schilder's disease, Gerstmann syndrome, multiple sclerosis, cerebro-cerebellar or corticobasal degeneration, metabolic disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, dementia with spastic paraplegia

- **dementia not associated with other pathologies, characterized by neurological signs frequently associated with:** cerebral abscesses, secondary or primary brain tumors, diffuse Lewy body disease, Marchiafava-Bignami disease, Binswanger disease, progressive multifocal leukoencephalopathy, cerebral vasculitis, viral encephalitis, granulomatosis, normotensive or obstructive communicating hydrocephalus, craniocerebral trauma, multiple cerebral infarctions of embolic or thrombotic nature

Staging

Defined by its complexity and heterogeneity, with multiple stages of degeneration and a rate of decline that varies from individual to individual, AD was classified in 2011 into three stages: the preclinical stage, characterized by subtle and barely noticeable cognitive deficits, and the active stage of the disease with rapid and progressive deterioration.

Thus, during the preclinical stage, diagnosis is typically made only through biochemical or cellular tests that detect specific markers in cerebrospinal fluid (CSF), such as decreased levels of Aβ42 peptides and increased levels of TAU proteins, as symptoms are not yet manifest. It is estimated that approximately 30% of the population may be in this stage. Clinical studies and research conducted on a cohort of 2,000 patients in 2012 revealed that this asymptomatic phase can be further divided into three primary categories and two secondary categories, based on clinical and biochemical criteria:

- Stage "0": this stage encompasses individuals who are predicted to develop Alzheimer's disease (AD) in the future but currently show no specific biomarkers and are asymptomatic at the time of assessment ("cognitively normal")—a secondary, supplementary category
- Stage "TSAC": this stage includes patients who exhibit normal levels of β-amyloid but have detectable specific biomarkers—another secondary, supplementary category Stage I of the Preclinical Phase: This stage corresponds to the period during which β-amyloid plaques are forming and accumulating.
- Stage I of the Preclinical Phase: this stage involves the formation and accumulation of β-amyloid plaques in the brain
- Stage II of the Preclinical Phase: Characterized by the onset of neuronal degeneration processes and the emergence of synaptic dysfunctions.
- Stage III of the Preclinical Phase: Marked by subtle memory inconsistencies and mild cognitive disturbances.

In the second stage, initial cognitive deficits become evident, signaling the onset of neurodegeneration. The third stage, however, is where AD is officially recognized in the medical field and diagnosed, as it is at this point that individuals with chronic neurodegenerative disorders are identified and their condition is confirmed. [1,2,13–15]

If a patient is diagnosed with early-stage cognitive impairment, they are classified under minor neurocognitive disorders according to DSM-5 standards. In contrast, patients with AD in moderate, advanced, severe, or terminal stages fall into the category of major neurocognitive disorders. [13,16–18]

The most commonly used clinical staging is based on the evolutionary phase (normal, mild, moderate, severe) (Figure 2) and the age of onset of cognitive symptoms (early-onset or late-onset). This is followed by the consideration of potential familial transmission, genetic risk factors, specific chromosomal anomalies, according to the 2015 publication titled "Everything About Alzheimer's." The prevalence of early-onset Alzheimer's disease (AD) is reported as 40 cases per 100,000 individuals aged 40 to 65 years, or 5 cases in the rare instance of genetic determinism. In contrast, there are 5,000 new cases reported per

100,000 individuals over the age of 65. The author estimates a prevalence of approximately 1% for the Romanian population, given the lack of specific national studies and statistics.

The most widely used clinical staging system categorizes Alzheimer's disease (AD) based on its progression through different phases (normal, mild, moderate, severe) (see Figure 2) and the age of onset (early-onset or late-onset). This classification also considers the potential for familial transmission, genetic predispositions, and specific chromosomal abnormalities. According to the 2015 publication "Everything About Alzheimer's," early-onset AD has a prevalence of approximately 40 cases per 100,000 individuals aged 40 to 65, with only 5 cases attributed to rare genetic determinism. In contrast, late-onset AD affects around 5,000 new cases per 100,000 individuals over the age of 65. The author estimates a prevalence of about 1% in the Romanian population, although there is a lack of concrete national studies and statistics to confirm this estimate. [13,19]

The classification based on the degree of cognitive decline includes four forms of Alzheimer's disease (AD), as established by the 2020 study published by Calabro M., et al.:

➢ Preclinical Stage

In this stage, patients are generally asymptomatic with no visible signs, and their daily activities remain unaffected. However, there are exceptions where some individuals may exhibit mild cognitive impairments. This initial phase is characterized by the onset of pathological changes in the entorhinal cortex and progresses with alterations extending into the hippocampus by the end of the preclinical stage. [17,20,21]

Mild Stage

This phase begins with observable changes in the cerebral cortex and is marked by noticeable cognitive decline. Symptoms include short-term memory loss, diminished problem-solving abilities, personality alterations, loss of spontaneity, sudden mood swings, confusion, spatial and temporal disorientation, impaired judgment and executive functions, and difficulty retaining new information. [17,20,21]

Moderate Stage

In the moderate stage, cognitive deficits deepen and affect areas of the cortex responsible for sensory processing, reasoning, and language. This phase is characterized by speech disturbances, behavioral issues, apathy, a tendency toward social withdrawal, and impaired visual and spatial orientation abilities. By the end of this stage, individuals may experience difficulty recognizing loved ones. [17,20,21]

Severe Stage

In the severe stage, pathological lesions extend throughout the entire cortex, leading to a profound loss of identity and independence. Patients exhibit significant motor coordination issues, including apraxia, akathisia, and dystonia (extrapyramidal motor signs). Additionally, symptoms such as insomnia, agitation, olfactory dysfunctions, anxiety, depression, and psychotic manifestations including delusional thoughts and hallucinations become evident. [17,20,21]

Diagnosis of AD, a Neurodegenerative Disorder

In order to facilitate a multidisciplinary approach and streamline the complex diagnostic process for differentiating types of dementia, determining the stage, and simultaneously ensuring access to accumulated patient data and medical procedures, a comprehensive medical file is created during the initial admission or consultation at any specialized center (whether a private practice, clinic, hospital). This file is initiated with the completion of the "General Clinical Observation Sheet" and is continuously updated

by clinicians and specialists. Throughout the investigation process, various documents such as forms, reports, medical letters, and original or copied results are attached to the file.

The establishment of a definitive diagnosis of Alzheimer's disease (AD) and the initiation of a therapeutic regimen tailored to the identified stage of disease progression will follow the definition of the predominant clinical picture, differential diagnoses, and the expertise of the attending physician, specialist, and primary care team. This process involves the completion of the following investigations and examinations, with the order determined by observations made during patient consultations with dementia syndrome:

To establish a definitive diagnosis of Alzheimer's disease (AD) and initiate an appropriate treatment plan based on the identified stage of progression, several key steps must be followed. These include defining the dominant clinical presentation, conducting differential diagnoses, and leveraging the expertise of the attending physician, specialist, and medical team. The process involves performing a series of investigations and examinations, with the specific order of procedures being determined according to the observations made during patient consultations for dementia: patient history, anamnesis, general clinical examination – somatic state, neurological examination, clinical cognitive assessment, neuroimaging investigations (MRI, CT, SPECT, PET), laboratory tests, psychiatric examination [e.g., consciousness, perception, verbal fluency, behavior, psychomotor activity, reality orientation, facial expression (mimics), eye expression, attention, memory (visual, short-term/long-term, operational, logical, auditory, semantic), thinking (irrational/rational, integrative, concrete/abstract, slow/fast), intellect, temperament, will, emotional range], mental health status testing, neuropsychological examination, CSF examination - cellular and biochemical analysis, electroencephalogram (EEG), brain biopsy.

Genetic Counseling in Alzheimer's Disease

When neurological symptoms emerge, specialists rely on the NINCDS-ADRDA or DSM-V-TR criteria to establish a definitive diagnosis of Alzheimer's disease. These criteria help determine the severity of cognitive decline and distinguish between probable and possible etiologies. The diagnostic criteria include the following characteristics in the absence of other neuropsychiatric or systemic conditions: insidious onset, unchanged consciousness (the patient's awareness and consciousness remain intact), progressive cognitive decline that affects at least two distinct cognitive domains, gradual behavioral changes, where the behavioral decline precedes cognitive one, resulting in multiple disturbances, typical amnestic presentation that includes impairments in learning and memory processes, the appearance of aphasia variants that may involve spatial-visual or primary progressive logopenic aphasia, which are considered non-amnestic and abnormal, and the age of onset: typically between 40 and 90 years. In moderate stages of Alzheimer's disease, deficits may be observed in areas resposable for the executive functions, perceptual-motor skills, semantic memory, language, learning ability, expression, social cognition, and complex attention. In severe stages, symptoms are often accompanied by additional impairments, including agnosia, apraxia, and aphasia.

A possible diagnosis of Alzheimer's disease (AD) is established by meeting specific clinical criteria and evaluating the patient, while a probable diagnosis offers the highest level of certainty. This higher certainty is based on the clinical presentation, evaluations, examinations, and tests, which are further supported by the identification of familial genetic predispositions, such as risk alleles (APOE ε4) or autosomal-dominant (APP, PSEN1, PSEN2) or recessive mutated genes (APP - A673V), confirmed through genetic testing of affected family members or by autopsy findings. The certainty of an AD diagnosis is strengthened by PET imaging results that may reveal β-amyloid or TAU protein accumulations, as well as

CSF analysis. Other key factors that support a probable diagnosis include a positive family history, abnormal CSF findings, elevated or normal percentage of slow wave activity on EEG, evidence of cerebral atrophy on brain imaging, and positive neuropathological confirmation. Additionally, symptoms such as myoclonus, hypertonia, gait disturbances, coordination issues, disorientation in advanced stages, and various neuropsychiatric symptoms like emotional, verbal and motor paroxysms, behavioral disturbances, depressive states, delirium, hallucinations, insomnia, weight loss, incontinence, and agitation contribute to the probable diagnosis. Conversely, the diagnosis is considered less probable or more doubtful (the level of uncertainty or skepticism about the diagnosis of AD increases) in the presence of epilepsy or seizures, hemiparesis, early sensory impairments, difficulty in spatial and temporal orientation, a sudden, apoplectic onset of symptoms, or early motor disturbances. These criteria align with guidelines established by the Romanian Ministry of Health and the Moldovan Ministry of Health, Labor, and Social Protection including the "Diagnostic and Treatment Guide for Dementias" issued by Romanian specialists and the "National Clinical Protocol for Dementia" published in the Republic of Moldova. [3,16–18,22,23]

Alzheimer's, being a multifactorial neurodegenerative disorder, involves a complex interplay between genetic and environmental factors, influenced by the time and the level of exposure, and genetic predisposition through the additive effects of the involved genes. This makes genetic counseling in a specialized clinic, under the attentive guidance of a medical geneticist, an essential and often mandatory step in both diagnosing patients with specific symptoms and during screening processes. Individuals, whether they have a family history of AD or not, may seek genetic counseling to determine their genetic predispositions and the risks of developing neurodegenerative diseases. This counseling can be recommended by a healthcare provider or requested by the individual, whether they are sick or healthy, to assess the risk of recurrence, establish a potential presymptomatic diagnosis, or gather information for families where multiple relatives have been diagnosed with LOAD or EOAD. The genetic consultation aims to provide valuable information, recommendations, and advice that can help delay the onset of AD, reduce exposure to environmental risk factors, enhance cognitive reserves, establish a prognosis, or understand specific details for early detection and the initiation of therapeutic interventions. It is also crucial for couples, whether premarital, preconceptional, prenatal, or postnatal, to seek genetic counseling for informed decision-making. [3,6–10]

In genetic counseling, identifying hereditary components is crucial, though often challenging. The presence of these components may be suggested by detecting some of the following characteristics: varying frequency in different populations, chromosomal abnormalities, genealogical transmission, familial distribution, identical traits in monozygotic twins, the presence of abnormal proteins, and associations with genetic markers. Genetic components form the basis of hereditary traits, being extremely significant in some cases and barely detectable in others. The specified criteria, when considered individually, do not hold absolute value nor do they allow for the determination of a trait's nature. The hereditary nature of traits can only be confirmed when several characteristics are identified simultaneously. Genetic counseling is a complex and specialized medical process in which the geneticist plays a central role within a collaborative, multidisciplinary approach. The primary objectives of genetic counseling include: establishing the clinical diagnosis with a high degree of precision, accurately determining the genetic causes (etiological diagnosis), preventing morbidity, and identifying hereditary components (clarifying the role of genetic factors). Additionally, the counseling aims to provide genetic advice by assessing the risk of recurrence of the neurodegenerative disease, evaluating potential treatment options to delay the disease's onset, offering care strategies, and identifying methods to mitigate risks or prevent

the condition. It also involves educating patients and families about the specific characteristics of AD, including prognosis, consequences, and stages of progression. [8,9,24]

In the case of a request made by a patient previously diagnosed with AD (proband), genetic testing will primarily aim to inform the family about the genetic origin of the condition. Secondarily, the objective will be to obtain specific additional information necessary for inclusion in research studies and candidacy for clinical trials evaluating various treatments, with the goal of mitigating the rate of cognitive decline.[24,25]

Genetic counseling requires the application of specific principles and methodologies, and is conducted in a stepwise manner within specialized medical genetics centers to address patients' needs. The process typically includes:

I. Recording personal data, establishing the reason for the medical consultation or admission

The registration of personal data, which must be kept confidential (including first name, last name, date of birth, personal identification number, identification series, residence, sex, age, occupation, and insurance status), along with the rationale for the consultation, and the potential establishment of a referral or admission diagnosis, are crucial steps. Following the archiving of medical records, these sections are essential for understanding the case should the medical documents be reviewed subsequently.

This stage serves as a period of acclimatization, focusing on establishing relationships between the patient, their accompanying individuals, and the physician. The physician will carefully observe their behavior while reviewing the objective elements in the previously compiled medical records. Interactions between the geneticist and the patient will occur in a calm and reassuring environment designed to foster trust and encourage collaboration. This approach aims to alleviate any anxiety the patient may have, facilitating the identification of major issues, the reason for the consultation, and all necessary information through open dialogue.

An essential component of evaluations designed to ascertain genetic predispositions to AD involves having the applicant accompanied by a family member, partner, or close associate. This person is crucial for supplying additional comparative information and for validating or challenging the accuracy of the patient's provided details.

In the sections addressing the reasons for hospitalization or consultation with the geneticists, a hierarchical assessment of the symptoms will be conducted. This includes the systematic organization and chronological arrangement of all observed signs, as well as documenting the progression and gradual development of cognitive decline.

II. Anamnesis

One of the decisive factors in establishing a differential diagnosis and formulating specific recommendations is anamnesis. The information gathered during this stage leads to the determination of the etiology of the dementia syndrome. Therefore, anamnesis will include the following steps during the genetic consultation: identifying heredocolateral history, recording personal, pathological, and physiological history, and establishing work and living conditions. The comprehensive collection of risk factors, susceptible genes, personal and familial antecedents, and predispositions is fundamental to the onset of AD, moving beyond the stage of vulnerability. Recording these factors in databases is essential in the genetic consultation process, which focuses on reconstructing the history, and establishing both familial and personal anamnesis.

- **Heredocolateral Anamnesis**

In the section dedicated to heredocolateral history, all information regarding the health status of the patien-

t's family, especially first-degree relatives (parents), is recorded. This information is subsequently used for diagnostic purposes, calculating recurrence risk, formulating and implementing genetic testing strategies, and identifying relatives with increased susceptibility and risk of developing AD. Collected from the patient upon admission or during the initial consultation and revisited at each follow-up consultation, heredocolateral history is particularly important when there is a high risk of recurrence of Alzheimer's neurodegenerative disease. This history, defined as the collection of social and biological relationships, physiological and mental states of at least three generations within the studied family, must be reconstructed effectively, with a high degree of accuracy, caution, and respect. Ethnic, cultural, religious, and socio-economic aspects should be considered, as the family history may carry significant emotional and psychological weight.

The absence of proper medical conduct, the use of inappropriate techniques, and low levels of culture, education, or intellectual capacity to receive and understand information of those investigated can significantly affect the accuracy of heredocolateral anamnesis. This also includes issues such as concealment of deviations from paternity, loss of contact with relatives, adoptions, fostering, the emergence of new mutations, recessive diseases, phenocopies, multifactorial diseases, omission of consanguinity details, premature death of relatives (for familial Alzheimer's disease—death of relatives under 60-65 years of age before the onset of specific symptoms—prevents the observation of a potential onset in the seventh or eighth decade of life), or multiple partners. These factors can result in a negative, inconclusive, and non-informative heredocolateral anamnesis in relation to the genetic condition under investigation. Additionally, an anamnesis may be deemed negative and non-informative if no heredocolateral antecedents are identified, indicating a sporadic case. However, if there is useful information about the family (such as the paternal grandfather, mother, or father) related to consanguinity or an X-linked disease, this can still be relevant even if the patient is the only diagnosed case.[6,8–10,24,25]

The professionalism, precision, specialized training, and psychological skills of the geneticist or the team of diagnostic specialists are attributes acquired over time through accumulated experience. These attributes are fundamental to conducting heredocolateral anamnesis under optimal conditions. A thorough examination, mastery of the techniques used, and allocation of sufficient time for discussions, particularly with the first- and second-degree relatives of the patient or proband, are essential for an accurate and effective assessment.

Reconstructing the family history while ensuring confidentiality in a disturbance-free environment is a crucial step in uncovering familial antecedents of neurodegenerative diseases (predecessors with familial LOAD or EOAD), particularly when the consultation request comes from a patient suspected of having AD. Establishing a family history of AD during familial anamnesis indicates the potential for detecting hereditary transmission of gene mutations or risk alleles from ancestors to descendants (as multiple individuals with AD may be identified over their lifetimes), whether through maternal, paternal, or both lines, or may reveal the possible influence of socio-economic, cultural, and environmental factors. This detailed anamnesis will thus highlight either the predominant influence of environmental factors, given the multifactorial nature of the condition, or, conversely, the major role of genetic factors in the etiology of AD.

Based on the information gathered from interviewing the patient/proband and their family, and to streamline the process, the medical evaluation will continue with the graphical representation of the concepts in the form of a family tree. This will be considered an official medical document, standardized,

and will use international conventional symbols. The legend will include all symbols and abbreviations used, and the header will contain the patient's identification details, the date, the specific code of the genetic consultation performed, the name of the examiner, the participants who provided conclusive information, as well as other relevant data such as the occurrence of consanguinity.

- **Personal Medical History**

This section includes the individual's life history with a focus on the specific disease under study, namely Alzheimer's disease (AD), detailing the reported manifestations, type of onset, clinical and paraclinical evaluations, and test results. Personal, physiological, and pathological antecedents facilitate differential diagnosis and help rule out possible non-genetic causes, thereby eliminating diseases that could lead to the development of a dementia syndrome.

In this stage of the interview, the patient is required to disclose any associated conditions they suffer from, including secondary diagnoses that could lead to the development of a reversible dementia. Such conditions may include: subdural hematoma, brain tumors, ischemic cardiomyopathy, valvulopathies, hypertension, paraneoplastic syndromes such as limbic encephalitis, normal pressure hydrocephalus, autoimmune diseases, metabolic disorders (chronic hypoglycemia, chronic liver and renal failure), hyperlipidemia, hypothyroidism or other endocrine disorders (Cushing's syndrome), peripheral atherosclerosis, and Wilson's disease. Additionally, the patient, who is often also the proband, should specify if they have had infections (such as tuberculosis, parasitic infections, encephalitis, meningitis, syphilis, or AIDS/HIV), if they have been informed of any vitamin B12 or folate deficiencies, or if they have been diagnosed with deficiency syndromes such as Wernicke-Korsakoff syndrome or pellagra through blood tests. The patient should also report any exposure to toxic substances (such as alcohol, lead, manganese, mercury, carbon monoxide, pesticides, lithium, or cocaine) or if they have taken medications categorized as high-risk (including tricyclic antidepressants, opioids, hypnotic sedatives, benzodiazepines, antihistamines, anticholinergics, proton pump inhibitors, trihexyphenidyl, or barbiturates).

- **Living and Working Conditions**

In addition to the risk factors encountered during work or daily life, the patient's behavioral activities, which are crucial for personal anamnesis, should also be documented. This category includes harmful activities such as chronic alcoholism, smoking habits, exposure to aluminium, organic solvents, pesticides, and other chemical/toxic substances, as well as drug use. These factors could significantly increase the risk of developing AD (Figure 3).
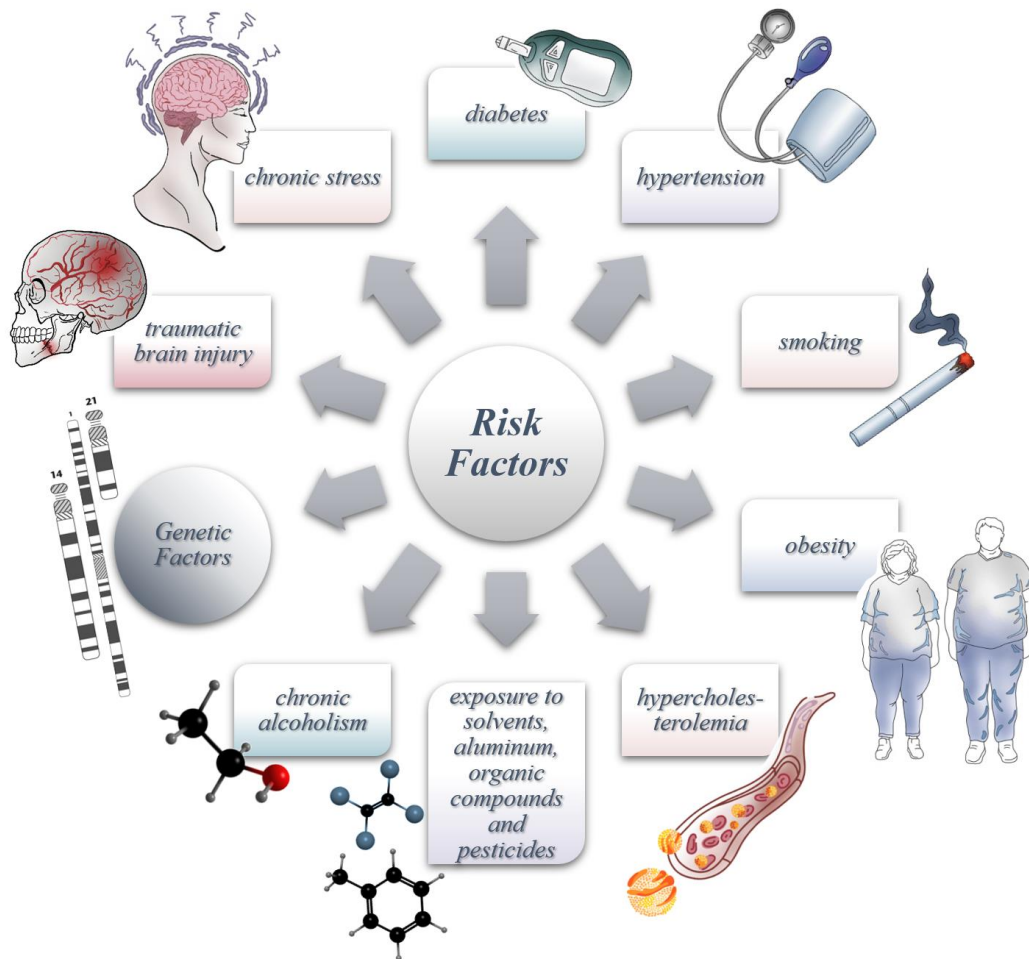
Figure 3 GENETIC (APP, PSEN1, PSEN2) and NON-GENETIC, modifiable risk factors (behavioral, pathological,physiological, and environmental) that contribute to the onset of AD [3]

III. Objective Clinical Examination

In accordance with established standards, the clinical examination must be conducted in strict adherence to published guidelines, ensuring accuracy and meeting the following conditions:

- It should be performed by multidisciplinary or interdisciplinary teams, particularly in cases of patients with cognitive disorders such as AD. The process requires close collaboration among specialists with diagnostic expertise, with the geneticist serving as the central figure who will ultimately draw the final conclusions within the genetic consultation.

- A thorough and perfected understanding of both normal and pathological, morphologically, structurally, and functionally abnormal variants is essential.

- The examination should employ advanced techniques of palpation, inspection, and percussion, mastered in their entirety by the specialists involved.

- It must be comprehensive, complex, conducted with the utmost seriousness, meticulousness, and attention to detail. The process should be methodical, systematic, and carried out in a staged manner to avoid overlooking potential etiologies or critical aspects, with sufficient time allocated for each step.

- Multiple photographs should be taken during the examination to objectively capture the reality of the patient's condition, highlighting symptoms and documenting visible signs as they emerge. These

images should be systematically archived in the patient's medical records. For patients with AD, these records should include the results of neuroimaging investigations, which will be compared over time to document changes, particularly in cortical regions, such as atrophy of the lobes and hippocampus or enlargement of the ventricles.

- The examination should describe, with a high degree of specificity, precision, and accuracy, both minor and major alterations observed, using appropriate and exact terminology.

The protocol to be followed will begin with a neurological examination, which will be the first step. If behavioral or non-cognitive disturbances are detected, a subsequent psychiatric evaluation will be conducted. Additionally, multiple assessment tests will be administered, including standardized scales to evaluate cognitive decline and, naturally, the state of depression as part of neuropsychological examinations.

IV. Paraclinical Explorations

This extensive category encompasses all essential paraclinical explorations necessary for diagnosing and differentiating AD(characterized by permanent and progressive dementia) from other diseases that may present with symptoms specific to dementia syndrome. At this stage, patients may undergo multiple neuroimaging investigations to rule out possible cerebral pathologies and confirm a suspicion of AD. Specialists may recommend performing brain computed tomography (CT) scans without contrast, with these scans repeated at a predetermined interval for comparative purposes, or non-invasive imaging investigations utilizing magnetic resonance imaging (MRI), with or without contrast agents. For differential diagnosis, a cerebral SPECT scan is also advised, always accompanied by either a CT or MRI, since the former technique has a generally low recommendation level (Level B) for distinguishing AD-type dementia from vascular dementia. In differentiating AD from FTD, the results of SPECT and PET scans will be analyzed, with the primary difference between these two etiologies being the presence of hypoperfusion in the anterior cerebral cortex in FTD and bilateral hypoperfusion in the parietal and temporal regions in AD. Paraclinical explorations also include serological tests, laboratory analyses, brain biopsy, CSF examination, EEG, APOE genotyping, genetic testing, identification of mutations in the APP, PSEN1, and PSEN2 genes, and screening for possible infections (HIV/AIDS, syphilis, tuberculosis, meningitis). [1,2]

In laboratory diagnostics, the following aspects should be monitored: routine tests such as a complete blood count (CBC), electrolyte panel, glucose, urea, creatinine levels, liver transaminases, and erythrocyte sedimentation rate (ESR) determination; identification of deficiencies in vitamins B12, B6, B1, and folates through serum testing; toxicological investigations to determine potential exposure to (or intoxication from) heavy metals such as As, Au, Mn, Hg, and Bi; molecular biology department tests to identify familial AD through genetic mutations on chromosomes 1, 14, and 21, and LOAD by APOE genotyping (specifically identifying alleles on chromosome 19 - 19q13); immunological tests targeting the diagnosis of autoimmune diseases such as systemic lupus erythematosus or vasculitis; detection of infectious diseases through serological testing for conditions like hepatic encephalopathy, syphilis, AIDS/HIV, and Lyme disease; assessment of thyroid function including tests for TSH, FT3, and FT4. [24–27]

According to the recommendations outlined in national guidelines, although the EEG holds a grade B recommendation at the international level—meaning its contribution to diagnostic accuracy lacks a high degree of certainty and reliability—it is nonetheless included as an additional investigation in the differentiation of AD from possible encephalitis or dementia caused by CJD. CJD is characterized by the accumulation of abnormal prion aggregates (amyloid plaques), which are proteins that have been

transformed into infectious agents due to genetic mutations induced by contact with abnormal, misfolded proteins. EEG is recommended because it reflects neuronal activity through the electrical activity of the underlying cerebral cortex. In cases of AD, EEG typically reveals a slowing of beta wave rhythms and an increase in the frequency of slow waves, with these changes being correlated with the loss of intellectual capacities. [2,16–18,23]

In differential diagnosis, CJD, which is associated with myoclonus and characterized by a rapid, progressive, and irreversible onset, can also be distinguished from AD, which has a more gradual progression, by identifying the 14-3-3 protein in the CSF. This test holds the same level of recommendation—grade B—in terms of diagnostic utility.

Another rare and additional investigation is the brain biopsy, which is only recommended when an etiological diagnosis cannot be established through other procedures. This procedure is performed after a decision by an extended committee of specialists from various disciplines and with the consent of the patient's family representatives, legal representative, or curator. It is conducted within neurosurgery centers due to its high risk and potential complications.

Testing the cellularity and biochemical characterization of CSF is particularly indicated in patients with AD. This testing typically reveals a low level of Aβ42 peptide and, in contrast, a significantly elevated level of TAU proteins compared to normal values observed in individuals without any form of AD or dementia.[28]

V. Analysis, Synthesis, and Interpretation of Data

The establishment of an etiological and clinical diagnosis will be preceded, as a mandatory step, by a phase of analysis and interpretation. In the case of AD, the diagnosis is not immediate but analytical in nature. It involves an interpretive approach that requires the validation, collection, correlation, and logical organization of data based on the specialist's experience and expertise.[9,29]

VI. Establishing the Diagnosis of AD

The diagnosis of AD, whether EOAD or LOAD, must be made with a high degree of precision and specificity. This process involves the integration of family and personal medical histories, general clinical examination, neurological and psychiatric assessments, and the results of all paraclinical, neuroimaging, and laboratory investigations. For patients with AD, diagnostic criteria from the NINCDS-ADRDA or DSM-V-TR guidelines should be applied. These criteria help determine whether the diagnosis is probable or possible, and they assist in establishing certainty, staging the disease, and evaluating the extent of cognitive decline, severity, and the rate of neurodegenerative processes.[16–18]

1. **Criteria for establishing a probable diagnosis of AD:**
- Deficits in at least two cognitive domains
- The outcomes from the Mini-Mental State Examination (MMSE) and the Blessed Scale should confirm the presence of a dementia syndrome
- The patient should be between 40 and 90 years old, with the highest incidence typically occurring between 60 and 70 years of age (~65 years)
- The disease should have an insidious onset with progressive, irreversible neurodegenerative processes leading to impairments in learning, memory, and various cognitive functions
- The patient's level of consciousness should remain intact
- Other potential neuropsychiatric or systemic conditions should not be identified or detected
2. **Criteria supporting a probable diagnosis of AD:**
- The patient experiences significant behavioral disturbances and difficulty adhering to routine daily

tasks / inability to perform daily activities

- Neuroimaging investigations confirm the presence of cerebral atrophy
- Aphasia
- Apraxia
- Agnosia
- Familial history of AD
- Confirmation of a family history of AD through genetic tests and neuropathological findings
- EEG: Slowed beta-wave rhythms and increased frequency of slow-waves
- CSF: Normal or low levels of Aβ42 (amyloid-beta peptide) and high levels of TAU proteins

3. **Criteria <u>supporting</u> the <u>probable diagnosis</u> of AD, when <u>other conditions</u> manifesting with cognitive, functional, or behavioral decline <u>have been excluded</u> (the etiological diagnosis of these conditions has been ruled out):**

- Intermittent plateaus (stagnation of progression) between periods of deterioration, continuous decline
- Onset of gait disturbances, hypertonia, and myoclonus
- Normal cerebral CT findings
- Weight loss in patients who were of normal weight or overweight at the time of diagnosis
- Onset of depressive states, insomnia, agitation, incontinence, delusions, or hallucinations
- Identification of agitation accompanied by motor, emotional, and verbal paroxysms

<u>Exclusion criteria</u> – <u>unlikely or doubtful diagnosis</u> of AD:

- Epilepsy (seizures)
- Sudden onset of the disease
- Early appearance of motor disturbances
- Identification of focal neurological signs: hemiparesis, inability to coordinate, objective sensory disturbances, visual field deterioration
- Infection with HIV/AIDS, meningitis, encephalitis, tuberculosis, neuroborreliosis
- Hypothyroidism, hypopituitarism, Cushing's syndrome
- Serological identification of deficiencies: vitamin B12, folates, pellagra, Wernicke-Korsakoff syndrome
- Familial hepatolenticular degeneration
- Hypoglycemia
- Prolonged hypoxia
- Chronic meningoencephalitis
- Exposure to heavy metals, pesticides, harmful/toxic substances, chronic intoxications
- Dialysis-related dementia
- Stroke (CVA), history of cerebrovascular diseases
- Brain tumors, multiple cerebral infarctions

Calculation of Recurrence Risk

As a multifactorial disease, Alzheimer's neurodegenerative disorder is recognized for its diverse determinants, encompassing genetic, non-genetic, epigenetic, environmental, and biochemical factors. The genetic risk associated with the onset of AD or other dementias, influenced by hereditary predispositions and environmental factors, manifests the following characteristics:

- In cases of EOAD, the transmission is mendelian, autosomal dominant, driven by mutations in the APP, PSEN1, and PSEN2 genes, with high penetrance. An exception is the A673V mutation in the APP gene, which is transmitted recessively.

- Neurodegeneration can be inherited, particularly in early-onset forms, where 35-60% of individuals have at least one first-degree relative affected.

- The risk of developing a non-mendelian early-onset form is contingent on the significant copy number of rare or common genetic variations, with concordance between the diagnosis of a patient and their descendants ranging from 2.5% to 50%.

- Approximately 80% of AD variants, the most common form of dementia, have a total or partial genetic etiology.

- The autosomal dominant inheritance pattern is identified in only 1-5% of all AD cases.

- Risk genes APP, PSEN1, and PSEN2 are responsible for up to 80% of familial, monogenic, dominant EOAD cases, with approximately 50% caused by mutations in presenilin 1 (chromosome 14 - PSEN1), 10-15% by mutations in the β-amyloid precursor protein (chromosome 21 - APP), and a small percentage by mutations in the presenilin 2 gene (chromosome 1 – PSEN2).

- In cases of sporadic LOAD, the transmission is heterogeneous, non-mendelian, and polygenic.

- The risk of developing LOAD is associated with the presence of the ε4 allele of the apolipoprotein E gene in 20-29% of cases, with the gene being encoded on the long arm of chromosome 19.

- The risk of initiating the neurodegenerative processes specific to LOAD increases approximately two to three times in individuals with the APOE ε3/ε4 genotype (heterozygous) compared to the general empirical risk, equating to about 10.4%. According to a study published by Goldman J.S. in 2012, 41% of Alzheimer's patients possess the APOE ε3/ε4 genotype, while only 21% of the healthy control group has this allele combination. The same study indicates that although the presence of a single ε4 allele increases the risk, 50% of those carrying this allele will not develop AD during their lifetime, underscoring that detection of this allele during genotyping is not sufficient for conclusive prediction.

- Conversely, studies show that the risk of developing LOAD increases by approximately 15-20 times in individuals homozygous for the ε4 allele (APOE ε4/ε4 genotype), with this risk being higher among women, as risk factors and susceptibility genes exhibit additive effects. The same study mentioned above found that 13% of individuals diagnosed with AD have two copies of the ε4 allele (homozygous for ε4), whereas this genotype is found in less than 1% of the healthy control group.

- The severity and progression of AD can vary within the same family (with the speed of progression differing from case to case). Compliance with medication, recommendations, and patient adherence can positively contribute to slowing the irreversible neurodegenerative processes typical of AD—classified under G30.0, G30.1, G30.8, G30.9, and associated mental and behavioral disorders in AD—classified under F00.0, F00.1, F00.2, F00.9. However, having a parent diagnosed with AD increases the proband's risk of developing AD by 2.5 times compared to an individual with both parents unaffected by AD.

- The recurrence risk is directly proportional to the number of affected relatives in a family when AD has a multifactorial determination. In cases of monogenic inheritance, the risk remains constant regardless of the number of diagnosed individuals.

- The risk of triggering neurodegenerative processes varies from one family to another.

- Patients severely affected by AD (with fulminant progression, early onset) have a significantly higher incidence of the disease among their relatives, indicating a strong genetic load. If AD has a higher prevalence in individuals of a certain sex, the recurrence risk will be higher among relatives of the less commonly affected sex.

- When multiple close relatives are affected by AD (both parents affected, one parent diagnosed along with at least two second- or third-degree relatives), the risk for other family members is high (~18%).

- The recurrence risk decreases rapidly among distant relatives, reaching its highest levels among close relatives, indicating that the risk is directly proportional to the degree of familial closeness, as evidenced by genealogical trees constructed during genetic counseling.

- An affected individual has a high risk, ranging between 2-5%, of having descendants with AD or dementia, compared to the general population.

- Furthermore, it is known that the risk of being diagnosed with AD can exceed 5% if multiple first-, second-, or third-degree relatives have been affected by neurodegenerative processes, if the affected individuals have severe, rapidly progressing variants, or if the individual belongs to a sex that is generally less affected by diseases more prevalent in one sex. [4,10,24,25,30–41]

Estimating the proportion of etiology attributed to genetic factors in relation to environmental and ecological factors is feasible, even though the susceptibility to a specific disease, such as AD, cannot be directly measured. This concept is defined as heritability. In this context, heritability (h^2) can be calculated to assess the extent to which genetic determinants contribute to the initiation of a disease or the manifestation of a multifactorial trait. The heritability coefficient is expressed as the ratio of the variation due to genetic factors (V_G—the additive effect of genes) to the total phenotypic variation observed (V_F): $h^2 = V_G / V_F$. Understanding the heritability value, which represents the proportion of genetic variation within the total phenotypic variation of a polygenic, multifactorially conditioned trait, is crucial not only for determining genetic susceptibility or predisposition to disease but also for preventing multifactorial diseases like AD, which have high heritability. This knowledge plays a significant role in tailoring preventive strategies and understanding the genetic underpinnings of complex diseases such as AD.

In the context of AD, genetic factors encompass multiple risk genes that exert minor yet additive effects, thereby inherently contributing to the development of disease susceptibility. The number of these genes is highly variable. Consequently, multifactorial determinism involves a complex and continuous interaction between environmental and hereditary components, characterized by polygenicity (the presence of multiple risk genes). The initiation of neurodegenerative processes may be activated or induced, in certain instances, in genetically susceptible individuals through exposure to specific environmental factors, thereby facilitating the transition to the onset of the disease and its associated symptomatology. The attainment and surpassing of the risk threshold are closely interdependent with the number of mutant genes (autosomal dominant mutations) and the allelic variants that an individual inherits through maternal, paternal, or both lines. The assessment of genetic risk in AD is calculated similarly to general risks, in accordance with the values provided in the recurrence risk table for multifactorial diseases. When empirical risks are unavailable, the values outlined in

Table *1* are used, which were previously determined based on the frequency in the population and the heritability of AD. This table is particularly useful for analyzing families with multiple members affected by AD. An important consideration is that the table does not account for relatives diagnosed with Alzheimer's dementia from the second, third, or fourth degree. Therefore, it is accepted that two affected

second-degree relatives, or multiple third- or fourth-degree relatives with AD, will be equivalent to one first-degree relative diagnosed with the disease. Consequently, if there is a single affected family member, whether from the first, second, third, or fourth degree, the risk can be estimated using

Table *1*.

Table 1. Recurrence Risks in Multifactorial Diseases – AD corresponds to a population frequency of 0.5% and a heritability of 60% [8,39,40]

Population Frequency (%)	Heritability (%)	Number of Affected Parents								
		0			1			2		
		Number of Affected Siblings								
		0	1	2	0	1	2	0	1	2
1	80	0.9	6.7	14.6	8.5	18.7	27.9	40.3	45.9	50.6
	60	1.0	4.9	10.6	5.7	12.3	19.2	21.7	28.3	34.1
	40	1.0	3.3	6.5	3.5	7.0	12	9.7	14.1	18.7
0.5	80	0.5	5.1	12.3	6.2	15.5	24.3	37.6	43.2	47.9
	60	0.5	3.4	8.4	3.8	9.5	15.8	18.1	24.4	30.0
	40	0.5	2.1	4.5	2.2	4.9	8.3	7.0	10.8	14.9
0.1	80	0.1	2.6	8.4	2.9	9.8	17.6	30.4	36.7	41.2
	60	0.1	1.5	4.6	1.5	5.0	9.6	11.5	17.1	22.2
	40	0.1	0.7	0.7	0.7	2.2	4.2	3.6	6.0	8.7

Calculating the Recurrence Risk is performed in accordance with the information provided by empirical risk tables for multifactorial diseases, taking into account a population frequency of approximately 1% and a heritability of 60% in Romania. [3,32,38–44]

Estimating Recurrence Risk begins with assessing the patient's health, especially when a family pedigree suggests a monogenic inheritance pattern, commonly seen in EOAD. If a heterozygous patient (Xx) marries a normal partner (xx), there is a 50% chance that their offspring will inherit the dominant gene and be diagnosed with the same condition (genotypic ratio: 1:1 – Xx, Xx, xx, xx). In scenarios where the individual consulting is homozygous for the dominant gene (YY) and the partner is homozygous for the recessive normal gene (yy), it is concluded that all offspring will be affected by the investigated disease (Yy). Conversely, if both parents are heterozygous (Zz), there is a 75% risk of having affected children (genotypic ratio: 3:1 – ZZ, Zz, Zz, zz). However, traits are not transmitted by an unaffected individual even if they come from a family with a pathological trait. In genetic counseling, factors such as gene expressivity and penetrance will be analyzed, considering the possibility of a trait being transmitted from an apparently normal patient in cases of polygenic, multifactorial inheritance specific to LOAD.

For autosomal recessive disorders (aa), the risk evaluation starts similarly with assessing health status and identifying carriers. When a carrier individual (Aa) marries a seemingly healthy but heterozygous partner

(Aa), the recurrence risk of the disease is approximately 25% (genotypic ratio: 1:3 – AA, Aa, Aa, aa). If previously diagnosed individuals (aa) marry normal, homozygous individuals (AA), all their direct offspring will be healthy but carriers (Aa). In unions with affected homozygous individuals (aa), 50% of the children will be affected (aa) (pseudodominance) and the remaining 50% will be healthy but carriers (Aa). In recessive gene transmission, if both parents are homozygous for the dominant gene (AA) or one parent is a homozygous non-carrier (AA) and the other is a heterozygous carrier (Aa), all offspring will be healthy, with 50% being carriers (genotypic ratio: 1:1 – AA, AA, Aa, Aa) in the second case.

In the specific case of chromosomal syndromes, it is rare for them to be caused by balanced translocations present in one of the two parents, as these anomalies are predominantly random. However, in this rare circumstance, it is necessary to consult the cytogenetics department/unit for parental testing (cytogenetic examination) if their offspring has a chromosomal syndrome with multiple malformations.

In multifactorial inheritance, the risk of transmission involves the presence of a vulnerability or predisposition to react unfavorably under the continuous influence of environmental factors, which may be harmful, or the development of neurodegenerative disorders. The recurrence risk is generally considered empirical in most cases, ranging between 2-4% in multifactorial transmission. This value depends on the frequency of occurrence of such neurodegenerative processes, including conditions like AD and early or late-onset dementias. In most specialized studies, the assessment of recurrence risk is based on empirical risks, values calculated according to the distribution of familial cases within a population.

Methodology for Providing Genetic Counseling in AD

In the comprehensive process of prophylaxis aimed at preventing the onset of multifactorial diseases such as neurodegenerative AD, the initial stages involve identifying affected individuals, detecting families with a "genetic predisposition" (autosomal-dominant or recessive inheritance, the presence of risk alleles), and calculating the recurrence risks of AD based on empirical risk tables. These steps are then followed by the formulation and provision of genetic counseling.

Genetic counseling, a complex and specialized medical process through which the risk of developing a multifactorial disease such as AD can be assessed—whether the disease is monogenic in the case of EOAD or polygenic in the case of LOAD, and whether it is fully or partially hereditary—serves multiple purposes. It is followed by the provision of genetic advice and is conducted under various circumstances, being sought in the following situations:

- **Premarital** – This type of consultation is rarely encountered in medical practice and occurs when both partners are aware that they carry mutations or risk genes, or when only one of them has a predisposition to develop AD, or they have close relatives diagnosed with hereditary forms of the disease. In such cases, they seek to identify the risk of their descendants being carriers, establish risks, and make presymptomatic diagnoses.

- **Preconceptional** – Generally, this type of genetic counseling is offered to a couple when the woman, as a prospective mother, is over the age of 35, has previously experienced spontaneous abortions, or is known to have reproductive disorders (infertility), or in the case of a consanguineous marriage. In this scenario, the mother's age represents a risk factor for conceiving a child with trisomy 21, as the presence of an extra copy of the APP gene inherently increases the risk of EOAD during the future adult's life who suffers from Down syndrome.

- **Prenatal** – This type of consultation is requested when prospective parents are aware of a significant "genetic burden" in the family, such as a history of confirmed familial AD, continuous or accidental exposure to risk factors (infections, medications, radiation, chemicals), or when there are suspicions or alarming signs during ultrasound/imaging evaluations or positive results in specific screening tests for a high-risk pregnancy.
- **Postnatal** or **Postmarital** – Genetic counseling is provided to new parents if their child is born with a genetic, chromosomal disorder, congenital anomaly, or if the parents express a clear desire to identify their child's genetic predispositions to adjust their lives accordingly, attempting to adopt a preventive approach. It is also recommended in the event of metabolic disorders, growth impairments, intellectual disabilities, or psychomotor impairments.

In all the aforementioned scenarios where genetic counseling is requested, the primary objective of providing advice, both before and after marriage, is to deliver accurate information regarding the risk of recurrence or the onset of the disease, to establish a prognosis, and, of course, to offer various options and treatment plans. To provide specialized consultation (neurological, genetic), establish a diagnosis, and formulate a prognosis regarding the progression of the neurodegenerative disorder (AD), the organizational framework should be represented by a suitable, specialized structure with multidisciplinary affiliations. This structure should facilitate a cooperative approach, with genetic counseling being provided in a staged manner throughout a complex process. [7,9,45]

Genetic counseling will commence with a phase involving both the establishment of a definitive and precise diagnosis through general paraclinical and clinical evaluations, and differential diagnoses conducted by diagnostic experts. This stage includes defining and outlining the characteristics of the identified neurodegenerative disorder and, if applicable, classifying cognitive, functional, and behavioral decline signs and symptoms within a specific evolutionary stage. This initial stage is crucial for the subsequent actions of genetic counseling, as without a concrete etiological diagnosis, the continuation of the medical process would be unfeasible.

The family history investigation as part of the anamnesis, along with genetic explorations, will lead to the identification of genetic characteristics (whether the condition, EOAD or LOAD, is genetic in nature). This process contributes to confirming the authenticity of lineage and represents the completion of the second stage of genetic counseling.

The third stage, which is crucial in the genetic counseling process, involves calculating the recurrence risk based on a thorough review of specialized literature and published articles. This stage includes adherence to empirical risk tables, as well as mendelian inheritance laws for dominant and recessive variants and non-mendelian principles for polygenic, multifactorial traits with additive effects. Following this, the data is interpreted and communicated to the consultant/proband, as well as their family or accompanying individuals.

The recurrence risk determined during genetic counseling is communicated to the family in a considerate manner. This communication is accompanied by detailed explanations tailored to the family's intellectual and educational level in the biomedical field. It is never conveyed to patients in a impersonal manner, such as through a standard genetic counseling report or template.

In the specialized literature, three categories of recurrence risk (R) are generally described:

- **Low Risk**: This category applies when the risk does not exceed approximately 10%.
  o **R < 10%**
- **Moderate Risk**: This category is for risks ranging between 10% and 25%.

- o **10% ≤ R < 25%**
- ▪ **High Risk**: This category is applicable when the risk of recurrence exceeds 25%.
- o **R ≥ 25%**

Considering the magnitude of genetic risk (r) and its percentage relative to empirical risk and the type of diagnosis, individuals are classified into one of the following categories based on the specialist geneticist's assessment:

- ▪ **Low Risk (r < 5%)**: Specific to a consultant with only one relative affected by AD.
- ▪ **Moderate Risk (5 ≤ r < 25%)**: Applies when one or both parents report having first-degree relatives previously diagnosed with the studied multifactorial condition with hereditary transmission (e.g., autosomal dominant or recessive conditions - EOAD).
- ▪ **High Risk (r ≥ 25%)**: This risk level is assigned when the disease has a monogenic determination, transmitted in an autosomal recessive manner, and the proband's parents are healthy carriers (heterozygous) of the risk gene.
- ▪ **Very High Risk (r ≥ 50%)**: Pertains to syndromic anomalies with dominant inheritance characterized by high penetrance.
- ▪ **Total Risk (100%)**: An extremely rare situation where an autosomal recessive syndromic anomaly is identified, and both parents are affected by the same anomaly, resulting in a complete recurrence risk.

The information and responses provided by the specialist must be personalized and tailored based on various factors, including the patient's age, intellectual capacity, level of formal education, ethical, political, religious, and moral beliefs, psychological balance observed in the family or couple, the severity of the disability, the presence of children or adolescents with manifested genetic predisposition, the degree of pregnancy or gestational age, the type of diagnosis, and therapeutic options. This personalization is crucial despite the fact that recurrence risk is calculated "objectively" and the prognosis should be conducted with impartiality.[6–9]

Upon receiving the objective and informed advice, along with additional explanations, the clients are the sole individuals capable of making decisions regarding the future of the pregnancy. Specialists and geneticists serve as informers, advisors, and guides, maintaining impartiality and not having the right to become emotionally involved, be subjective, or influence the decision-making process. However, prospective parents in the context of prenatal counseling should be aware that no pregnancy is risk-free, and certainty about the health of the future child cannot be guaranteed. Every female individual has a baseline risk of 1-2% of giving birth to a child with congenital abnormalities, and this percentage increases based on specific familial circumstances identified during genetic counseling. Any potential feelings of guilt or blame on the part of the parents should be alleviated through an objective explanation of the circumstances leading to the birth of a child with congenital malformations or genetic defects. According to the code of ethics, the geneticist is not permitted to establish a maximum acceptable risk level, even if such a question arises from the patients. Their role is solely to inform, assist, and guide prospective parents in making a rational decision. The geneticist acts as a compassionate and empathetic advisor, not a judge. Understanding the information provided by the geneticist and applying the new concepts to make decisions that align with the family's values and interests will ensure the successful completion of the genetic counseling process.[6–10]

Thus, it can be asserted that genetic counseling is based on the following ethical coordinates: ensuring a conducive psychological and ethical environment during the final stage of presenting calculated risks, educating the clients, their families, probands, and the general population, ensuring confidentiality of

personal data and histories, obtaining informed consent from both spouses involved, and extending professional secrecy to future parents in cases where the condition is minor. If a X-linked recessive genetic syndrome or disease is not identified, the sex of the future child will not be disclosed.

Although most authors advocate for a strictly informative, objective, and neutral stance during the risk communication process, without directly influencing the decision of the clients or parents, there are numerous controversies regarding how genetic counselors fulfill their duties. Their approach is not always considered to be entirely "non-directive."

According to information published in medical genetics manuals and textbooks (Figure 4), the geneticist has the responsibility to provide patients with information about the pathology identified through clinical and paraclinical evaluations, treatment options, and prognosis. They are obligated to calculate and communicate the recurrence risk of the condition to descendants or other family members during the consultation, while adjusting their approach to the client's understanding and needs. [9,10,46]

Conclusions

- **Importance of Accurate Diagnosis:** Effective management of Alzheimer's Disease (AD) relies on precise and early diagnosis, achieved through adherence to established diagnostic criteria such as the NINCDS-ADRDA and DSM-V-TR guidelines. Accurate diagnosis helps differentiate AD from other neurodegenerative disorders and allows for appropriate treatment planning and support.

- **Role of Genetic Counseling:** Genetic counseling is crucial in understanding the hereditary aspects of AD, particularly in differentiating between early-onset (EOAD) and late-onset (LOAD) forms. By evaluating family history and genetic risk factors, counselors can provide tailored advice and support to individuals and families, helping them understand their risk levels and making informed decisions about preventive measures and potential genetic testing.

- **Risk Assessment Methodologies:** Risk assessment involves a combination of genetic, environmental, and empirical data. Understanding the heritability of AD and utilizing empirical risk tables allows for a nuanced assessment of recurrence risks. This helps in categorizing risk into low, moderate, high, or very high levels, which is essential for personalized counseling and preventive strategies.

- **Personalization of Counseling:** The process of genetic counseling must be highly individualized, considering factors such as the patient's educational background, psychological state, and personal values. Effective communication of risk information should be clear, compassionate, and tailored to the needs of each individual or family.

- **Ethical and Psychological Considerations:** Ethical considerations in genetic counseling include maintaining confidentiality, obtaining informed consent, and providing unbiased information. Counselors should ensure that patients are aware of the limitations of genetic testing and risk assessment, and support them in making decisions that align with their values and circumstances.

- **Implications for Preventive Strategies:** Insights from genetic counseling and risk assessment can inform preventive strategies for AD, including lifestyle modifications and early intervention programs. Understanding individual risk profiles helps in designing personalized prevention plans and may contribute to better management and potentially reduced incidence of the disease.

- **Future Directions:** Continued research into the genetic and environmental factors influencing AD is essential for improving diagnostic accuracy and risk assessment. Advances in genetic testing and a deeper understanding of AD pathophysiology will enhance the effectiveness of genetic counseling and preventive strategies, ultimately contributing to better outcomes for individuals at risk of AD.
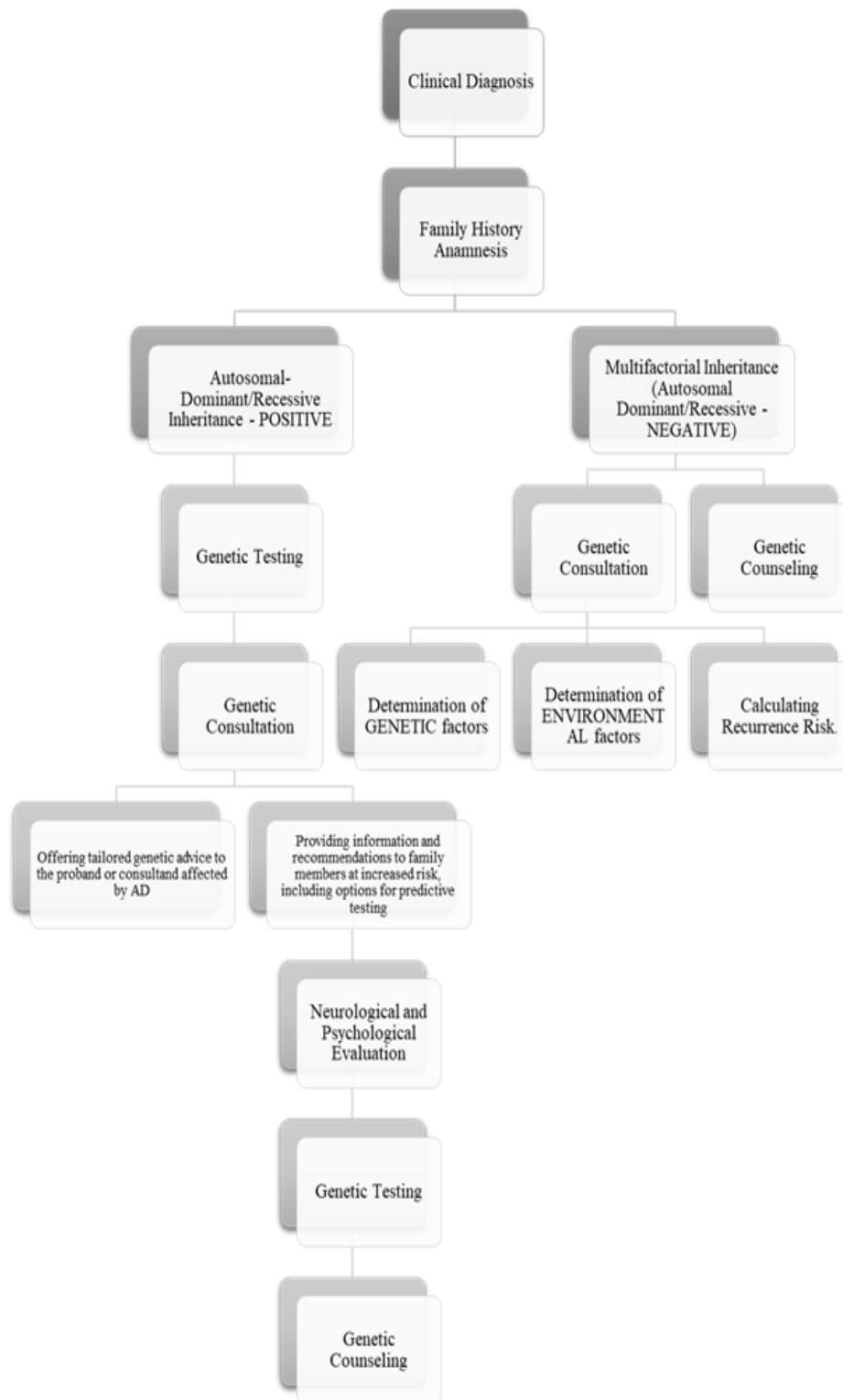
Figure 4. Genetic Exploration Protocol – Testing, Consultation, and Counseling [9,25]

- **Protocol for Exploratory Genetic Testing**: Testing for a proband with AD – Autosomal Dominant Transmission.
- **Protocol for Predictive Genetic Testing**: Sequence of steps for a symptomatic consultand considering genetic testing, followed by predictive counseling and genetic advice.

References

1. Szalontay AS. Actualități în boala Alzheimer. Iași: Editura Gr. T. Popa; 2014.
2. Szalontay AS, Chiriță V, Chiriță R. Boala Alzheimer - Management Clinico-Terapeutic. Iași: Editura U.M.F. "Gr.T.Popa" ; 2005.
3. Saragea PD. Alzheimer's Disease (AD): Environmental Modifiable Risk Factors. International Journal for Multidisciplinary Research (IJFMR). 2024 Aug 31;6(4):1–11.
4. Reitz C, Rogaeva E, Beecham GW. Late-onset vs nonmendelian early-onset Alzheimer disease: A distinction without a difference? Neurol Genet. 2020;6(5).
5. Soria Lopez JA, González HM, Léger GC. Alzheimer's disease. In: Handbook of Clinical Neurology. Elsevier B.V.; 2019. p. 231–55.
6. Covic M. Curs de genetică medicală. Iași: Institutul de Medicină și Farmacie, Disciplina de Biologie si genetică medicală; 1981.
7. Covic M. Lucrări practice de biologie medicală. Iași; 1976.
8. Covic M, Stefănescu D, Sandovici I. Genetică medicală. Editura Polirom; 2004.
9. Covic M, Ştefănescu D, Sandovici I. Genetică Medicală. Polirom; 2017.
10. Tudose C, Maniu M, Maniu C. GENETICĂ UMANĂ. Iași: Editura CORSON; 2000.
11. Bird TD. Genetic aspects of Alzheimer disease. Genetics in Medicine. 2008 Apr;10(4):231–9.
12. Bird TD. Alzheimer Disease Overview. GeneReviews. 1998;1993–2023.
13. Stănescu A. Totul despre Alzheimer. Vols. I, II. Târgu Mureș: Farmamedia; 2015.
14. Societatea Română Alzheimer. BOALA ALZHEIMER.
15. Societatea Romana Alzheimer. Boala Alzheimer si dementele. 2006;
16. American Psychiatric Association. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS FIFTH EDITION - DSM-5-TR. Vol. V. 2022.
17. American Psychiatric Association. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH EDITION - DSM-IV-TR. 2010.
18. American Psychiatric Association. DSM-5-TR. 2022.
19. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol. 2018 Jan 1;25(1):59–70.
20. Calabrò M, Rinaldi C, Santoro G, Crisafulli C. The biological pathways of Alzheimer disease: a review. AIMS Neurosci. 2021;8(1):86–132.
21. Förstl H, Kurz A. Clinical features of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 1999;249:288–90.
22. Bellenguez C, Küçükali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet [Internet]. 2022 Apr 4;54(4):412–36. Available from: https://www.nature.com/articles/s41588-022-01024-z
23. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Rey Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. The Lancet [Internet]. 2007;6. Available from: http://neurology.thelancet.comVol
24. Goldman JS. Predictive genetic counseling for neurodegenerative diseases: Past, present, and future. Cold Spring Harb Perspect Med. 2020 Jul 1;10(7):1–15.
25. Goldman JS. New approaches to genetic counseling and testing for alzheimer's disease and frontotemporal degeneration. Curr Neurol Neurosci Rep. 2012 Oct;12(5):502–10.
26. Breitner JCS. Clinical Genetics and Genetic Counseling in Alzheimer Disease. Ann Intern Med [Internet]. 1991;115(8):601–6. Available from: https://annals.org/

27. Langlois CM, Bradbury A, Wood EM, Roberts JS, Kim SYH, Riviere ME, et al. Alzheimer's Prevention Initiative Generation Program: Development of an APOE genetic counseling and disclosure process in the context of clinical trials. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2019 Jan 1;5:705–16.

28. Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. Nat Rev Dis Primers. 2021 Dec 1;7(1).

29. Arias JJ, Lin GA, Tyler AM, Douglas MP, Phillips KA. Geriatricians' Perspectives on the Multiple Dimensions of Utility of Genetic Testing for Alzheimer's Disease: A Qualitative Study. Journal of Alzheimer's Disease. 2022;90(3):1011–9.

30. Barber RC. The genetics of Alzheimer's disease. Vol. 2012, Scientifica. 2012. p. 1–14.

31. Bruni AC, Bernardi L, Maletta R. Evolution of genetic testing supports precision medicine for caring Alzheimer's disease patients. Curr Opin Pharmacol. 2021 Oct 1;60:275–80.

32. Cannon-Albright LA, Foster NL, Schliep K, Farnham JM, Teerlink CC, Kaddas H, et al. Relative risk for Alzheimer disease based on complete family history. Neurology. 2019 Apr 9;92(15):e1745–53.

33. Goldman JS, Van Deerlin VM. Alzheimer's Disease and Frontotemporal Dementia: The Current State of Genetics and Genetic Testing Since the Advent of Next-Generation Sequencing. Mol Diagn Ther. 2018 Oct 1;22(5):505–13.

34. Goldman JS, Hahn SE, Catania JW, Larusse-Eckert S, Butson MB, Rumbaugh M, et al. Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genetics in Medicine. 2011;13(6):597–605.

35. Reyes-Domínguez YA, Figuera LE, Brambila-Tapia AJL. Perceptions of Knowledge, Disease Impact and Predictive Genetic Testing in Family Members at Risk to Develop Early-Onset Alzheimer's Disease (EOAD) and Their Levels of Suicidal Ideation: A Mixed Study. Brain Sci. 2023 Mar 1;13(3).

36. Roberts JS, Patterson AK, Uhlmann WR. Genetic testing for neurodegenerative diseases: Ethical and health communication challenges. Neurobiol Dis. 2020 Jul 1;141.

37. Ryan MM, Cox CG, Witbracht M, Hoang D, Gillen DL, Grill JD. Using direct-to-consumer genetic testing results to accelerate Alzheimer disease clinical trial recruitment. Alzheimer Dis Assoc Disord. 2021;35(2):141–7.

38. Silverman JM, Smith CJ, Marin DB, Mohs RC, Propper CB. Familial Patterns of Risk in Very Late-Onset Alzheimer Disease. Arch Gen Psychiatry. 2003;60(2):190–7.

39. Smith C. Recurrence Risks for Multifactorial Inheritance. Am J Hum Genet. 1971;23(6):578–88.

40. Smith MA. ALZHEIMER DISEASE. 1998;

41. Tosto G, Bird TD, Tsuang D, Bennett DA, Boeve BF, Cruchaga C, et al. Polygenic risk scores in familial Alzheimer disease. Neurology. 2017 Mar 21;88(12):1180–6.

42. Armstrong RA. Risk factors for Alzheimer's disease. Vol. 57, Folia Neuropathologica. Termedia Publishing House Ltd.; 2019. p. 87–105.

43. Bijanzadeh M. The recurrence risk of genetic complex diseases. Journal of Research in Medical Sciences. 2017;22(1).

44. Sharma VK, Mehta V, Singh TG. Alzheimer's Disorder: Epigenetic Connection and Associated Risk Factors. Curr Neuropharmacol. 2020 Jan 28;18(8):740–53.

45. Rentería ME, Mitchell BL, De Lara AM. Genetic testing for Alzheimer's disease: Trends, challenges and ethical considerations. Curr Opin Psychiatry. 2020 Mar 1;33(2):136–40.

46. Ion V, Georgescu Ș., Câmpeanu A, Tufănoiu E, Tudoran C, Lupescu I. Neurologie Clinică. Editura ALL; 1999. 1–608 p.