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Unlocking Alzheimer's: From Genes to Gut, A New Era of Hope

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Abstract
Alzheimer's disease (AD) and other dementias (ADODs) represent a growing global health crisis, with a near-doubled mortality rate from 1990 to 2021, affecting 57.4 million people and projected to reach 152.8 million by 2050. Characterized by amyloid plaques, tau tangles, and synaptic dysfunction, AD drives cognitive decline and disability, particularly in low- and middle-income countries. Advances in genetics, biomarkers, and imaging are revolutionizing early detection and personalized treatment. Genetic risk factors like APOE4 and emerging polygenic risk scores guide precision medicine, while biomarkers in cerebrospinal fluid, blood, and PET imaging enable preclinical diagnosis. Novel research on the gut-brain axis highlights microbial dysbiosis as a contributor to AD pathology, with probiotics and fecal microbiota transplantation showing promise. Despite progress, challenges like costly diagnostics, stigma, and ethical concerns around early diagnosis persist. This review explores these advancements, emphasizing patient-centered care and the potential of multi-modal strategies to slow or prevent AD progression, offering hope for a future where Alzheimer's is less devastating.

Keywords: Alzheimer's Disease, Amyloid Plaques, Tau Tangles, Synaptic Dysfunction, Biomarkers, Precision Medicine, APOE4, Polygenic Risk Scores, Gut-Brain Axis, Microbial Dysbiosis, Probiotics, Fecal Microbiota Transplantation, PET Imaging, Diffusion Tensor Imaging, Early Diagnosis, Disease-Modifying Therapies, Lifestyle Interventions, Health Disparities, Inflammation, Machine Learning, CRISPR Drug Repurposing

Introduction
Alzheimer's disease (AD) is a progressive neurodegenerative disorder, which is characterized by cognitive decline and memory impairment. It can be described as a significant global health challenge, affecting millions, especially older patients and their families but also caregivers and healthcare systems. Over the past two decades, the global burden of this Alzheimer's disease and other dementias (ADODs) has risen significantly, making it the primary contributor to functional decline and dependence among older adults [1]. An estimated number of 57.4 million people are affected by dementia worldwide, and projections indicate this number could increase to 152.8 million cases by 2050. This strong increase in numbers may be due to increasing life expectancy but also rising prevalence of certain dementia risk factors which have significantly contributed to the sharp rise in dementia-related mortality [2,3].

Since 1990, Alzheimer's disease and other dementias (ADODs) have become a growing global health crisis. The death rate from these conditions has nearly doubled, rising from 12.21 per 100,000 people in 1990 to 23.54 per 100,000 in 2021. This makes ADODs the fifth leading cause of death worldwide. Among neurological disorders, they rank as the second deadliest, trailing only stroke. About one in five people with a neurological condition have some form of Alzheimer's or dementia.

Beyond mortality, ADODs are a leading cause of disability, especially for adults over 60. They rob people of healthy years, contributing significantly to what experts call disability-adjusted life years (DALYs)a measure of time lost to illness or disability. In 2021, DALYs peaked for those aged 80-84, with women experiencing higher rates than men across all age groups.

The burden is particularly heavy in low- and middle-income countries, where two-thirds of people with ADODs live. Rapid population growth, poverty, and limited access to healthcare drive faster increases in cases compared to wealthier nations. However, even in high-income countries like Switzerland or the United States, where healthcare systems are robust, ADODs remain a significant challenge. Factors like education, income inequality, fertility rates, and healthcare spending shape these outcomes, highlighting the need to address health disparities.

In Romania, for example, the impact is clear. In 2021, the country reported between 98,681 and 254,345 DALYs due to ADODs, with a crude DALY rate of 707 to 922 per 100,000 people. When adjusted for age, the rate was 377 to 393 per 100,000. These numbers reflect a widespread issue that demands global attention. To tackle this crisis, we must invest in equitable healthcare, improve access in underserved regions, and address social factors like poverty and education. Only by working together can we reduce the devastating toll of Alzheimer's and other dementias [4].

Alzheimer's disease is a degenerative neurological condition that progressively affects a person's memory, cognitive abilities and behavior. This neurological disorder develops in stages, which can be characterized into a preclinical phase, then it progresses to mild cognitive or behavioral changes until it finally leads to Alzheimer's dementia. Recently, many healthcare specialists have been pushing for earlier diagnosis, before patients reach the dementia stage. An early detection and a more accurate understanding of the disease would be crucial for proper screening, diagnosis and, most importantly, treatment. Patients and their families but also caregivers could prepare better for the future and make the necessary lifestyle adjustments which can help to preserve quality of life for as long as possible. If Alzheimer's disease were diagnosed in an early stage, risk-reduction strategies could lead to significant improvements in cognitive, functional and behavioral deterioration. Additionally, early diagnosis will be crucial once therapies targeting the underlying pathology of Alzheimer's disease are approved. At the present, 19 biologic compounds are undergoing Phase 2 or 3 trials. Once approved, healthcare professionals will be able to integrate these into patient care, ensuring they help to maintain cognitive function and independence for longer than current treatments allow [5].

A Focus on Prevention

There's hope in prevention. Research shows that over 30% of AD cases might be linked to risk factors we can change, like diet, exercise, or managing conditions such as diabetes and high blood pressure. By focusing on these, we could delay memory decline or even lower the number of people who develop AD. Imagine if simple lifestyle changes could make such a big difference—that's the power of prevention [6].

The Brain's Protective Shield

One of the biggest challenges in treating AD is getting medicines to the brain. The brain has a natural defense called the blood-brain barrier, which acts like a security guard. It blocks harmful things like toxins and germs, keeping the brain safe. But this barrier also makes it hard for many AD drugs to reach the brain, limiting their effectiveness. It's a double-edged sword: the barrier protects us but also holds back potential treatments [6].

Looking Ahead

The fight against AD is more than just managing symptoms about finding new solutions and preventing the disease before it takes hold. By tackling modifiable risk factors and finding ways to get treatments past the blood-brain barrier, we can move closer to a future where Alzheimer's is less common and less devastating. Every step forward counts in this global effort [6].

The Role of Amyloid Plaques

Amyloid plaques are sticky clumps that form outside brain cells, primarily due to the buildup of a protein fragment called beta-amyloid. This fragment comes from a larger protein, amyloid precursor protein (APP), which gets chopped up by enzymes called β- and γ-secretases. Over time, these beta-amyloid pieces stick together, creating plaques that first appear in the neocortex (the brain's outer layer) and later spread to deeper areas like the hippocampus, subcortical regions, and even the cerebellum. Before they form plaques, beta-amyloid fragments exist as soluble oligomers—early, toxic versions that wreak havoc. They disrupt communication between brain cells, trigger inflammation, and cause oxidative stress, which damages neurons. This weakens the connections (synapses) between neurons, impairs their ability to send signals, and disrupts critical brain chemicals, all contributing to the memory and thinking problems seen in AD [7].

The Trouble with Tau Tangles

The second hallmark of AD is neurofibrillary tangles, caused by a protein called tau. Normally, tau helps stabilize the internal structure of brain cells, like scaffolding that keeps things in place. In AD, tau gets chemically altered (hyperphosphorylated), causing it to twist into abnormal tangles inside neurons. These tangles first form in the hippocampus, a key memory center in the temporal lobe, often long before symptoms show up. Over time, they spread to the outer temporal regions and other parts of the cortex, mirroring the worsening of AD symptoms. These tau tangles disrupt the transport system inside neurons, like clogging a highway. This blocks communication between brain cells and leads to cell death, causing the brain to shrink (atrophy) as the disease progresses [7].

Synaptic Dysfunction: The Early Warning Sign

Beyond plaques and tangles, AD heavily impacts synapses—the tiny connection points where neurons talk to each other. Synaptic damage is one of the earliest signs of AD and a major driver of cognitive decline. Tau plays a sneaky role here too. Abnormal tau can latch onto synaptic vesicles (the packets that release brain chemicals) and interfere with how synapses function. At first, this causes a burst of uncontrolled chemical release, driven by calcium leaking inside the cell. But over time, the synapses become suppressed, unable to release chemicals properly. Worse, certain forms of tau can cause synapses to swell and lose their supply of vesicles, further disrupting communication. This loss of synaptic connections starts early in AD, long before plaques and tangles fully take hold, and is a key reason why memory and thinking skills fade [7].

Genetic and Environmental Risk Factors

The APOE4 allele is recognized as the strongest known genetic risk factor for Alzheimer's disease, with those carrying a single copy facing a tripled risk, while individuals with two copies have up to 15 times the likelihood of developing the condition. However, beyond APOE4, genetic research has uncovered numerous other risk-associated loci, though their individual impacts are significantly smaller. However, according to data extracted from large scale genome-wide association studies (GWAS), multiple genes may contribute to disease susceptibility. To quantify the overall genetic risk, polygenic risk scores (PRSs) have been developed, combining the influence of multiple genetic variants into a single risk estimate. While these PRSs have shown some ability to differentiate individuals at higher risk for AD, their predictive strength does not always surpass that of APOE4 alone. Nonetheless, recent improvements in these models suggest they may enhance the accuracy of AD risk assessments when used in combination with other diagnostic tools [8].

Stages of Alzheimer's Disease

The preclinical phase of Alzheimer's disease refers to the period before cognitive symptoms become evident enough for a clinical diagnosis. If subtle, yet progressive changes in memory, reasoning or behavior emerge in individuals over the age of 55, considering the possibility of preclinical Alzheimer's could be valuable. The first signs of cognitive decline in Alzheimer's disease typically manifest as difficulties with episodic memory, which is linked to damage in the hippocampus, and challenges in executive function. Identifying this preclinical stage of AD can be challenging for healthcare professionals, however, it is crucial for neurologists and other primary care providers to be able to recognize the prodromal stage of AD, which includes mild cognitive impairment (MCI). In this stage, obvious symptoms of brain dysfunction are evident. Patients in the prodromal stage will show obvious short-term memory deficits and a noticeable decline in problem-solving abilities and decision-making skills. In later stages of MCI and the early phases of AD dementia, individuals experience challenges in preforming instrumental activities of daily living independently (like driving, working, shopping, etc.). These difficulties significantly impact their ability to function efficiently. The final stage is the dementia stage. These individuals experience noticeable, progressive memory loss, starting with short-term memory and eventually affecting long-term memory. They often misplace items and frequently repeat questions. Over time, they may struggle to recall the correct date, day of the week, and eventually even the month or year. As individuals progress from the mild to moderate stages of AD dementia, neuropsychiatric disturbances become more prevalent.

Advancements in Alzheimer's Management

Alzheimer's disease (AD) therapies should be administered in the preclinical stage, before significant neuronal damage or at the onset of mild cognitive impairment. Effective treatment requires biomarker panels to detect early pathology, classify disease stage, track progression, and predict decline. To identify such biomarkers, the study analyzed AD related changes in the cerebrospinal fluid (CSF) proteome [9]. The study identified structural changes in amyloid-β (Aβ) in blood, which correlate with CSF biomarkers and PET imaging. In a longitudinal cohort, this biomarker detected AD years before diagnosis with a likelihood ratio of 7.9, potentially serving as a first-line screening tool [10]. While cerebrospinal fluid biomarkers like Aβ1–42 and tau are well-studied, there is a growing need for less invasive, blood-based alternatives. This review explores proteins, lipids, metabolites, oxidative stress markers, cytokines, and emerging miRNAs and lncRNAs as potential AD biomarkers, along with vitamins and gut microbiome-related molecules for diagnosis and monitoring [11].

PET imaging enables in vivo tracking of AD pathology, including amyloid, tau, and microglial activation, and may aid diagnosis and treatment. While PET tracers can differentiate AD and MCI from healthy controls, limitations prevent a single optimal biomarker, prompting research into combined imaging approaches [12]. Early disease-modifying therapies could be most effective, making early diagnosis and monitoring essential. Imaging techniques, such as measuring hippocampal volume and amyloid-β (Aβ) accumulation, help in diagnosis, but Aβ may not be suitable for tracking disease progression. Tau accumulation measured with PET shows promise for early diagnosis and monitoring but needs large-scale validation. Although several biomarkers are useful for early diagnosis and tracking, limitations in specificity and reliability remain. Future research should focus on improving imaging techniques and discovering novel biomarkers for early AD detection [13].

Machine learning is being applied to identify metabolic diseases like AD and diabetes, with increasing incidence rates. Early-stage AD is difficult to predict, but early treatment is more effective. Techniques such as Decision Trees, Random Forest, and Support Vector Machines are used to predict AD using the Open Access Series of Imaging Studies (OASIS) data, with performance measured by metrics like Accuracy and F1-score. The proposed model achieves an average accuracy of 83%, outperforming existing methods and aiding early diagnosis to reduce mortality [14]. Initial treatments

aimed at improving brain perfusion, while newer drugs target neurotransmitter imbalances and disease progression. FDA approved treatments include BPSD mitigators (brexpiprazole, suvorexant) and cognitive decline mitigators (donepezil, rivastigmine, galantamine, memantine). Donepezil is widely used but requires cardiac monitoring, while memantine offers neuroprotection. Disease modifying drugs like aducanumab and lecanemab reduce Aβ burden but pose risks. Treatment decisions should consider drug availability, patient compliance, comorbidities, and non-pharmacological approaches [15]. AD treatment research is advancing, with 121 agents in clinical trials targeting neuropsychiatric symptoms, cognition, and disease progression. Most (80%) focus on disease modification, progressing through phase-1 to phase-3 trials. Biomarkers aid in participant selection, treatment monitoring, and safety assessment. Secondary prevention trials now include high-risk but cognitively normal individuals. Advances in targets, trial designs, and biomarkers are accelerating therapy development [16]. The FINGER trial demonstrated that a multidomain lifestyle intervention can help preserve cognitive function in at-risk older adults. To expand this research globally, the WW-FINGERS network was launched, adapting FINGER-type trials to diverse populations. This initiative fosters international collaboration, supports preventive strategies, and translates research into public health practice [17]. Alzheimer's disease (AD) is the leading age-related dementia, characterized by amyloid-β plaques and tau tangles, with current treatments offering limited symptomatic relief. Recent advances have led to disease-modifying therapies, particularly anti-Aβ monoclonal antibodies (mAbs) like aducanumab and lecanemab, targeting the underlying pathophysiology [18]. Aducanumab, a monoclonal antibody targeting amyloid β aggregates, became the first drug approved by the FDA for Alzheimer's disease in June 2021, based on its ability to remove Aβ plaques. However, the approval sparked debate due to inconclusive Phase 3 trial results and concerns over its efficacy, cost, and safety. The European Medicines Agency rejected it, and Biogen is conducting a confirmatory study, ENVISION, set to complete in 2026. Despite controversy, aducanumab's impact on tau pathology opens possibilities for combination therapies in AD [19]. anti-Tau monoclonal antibodies (HJ8.5, HJ9.3, HJ9.4) were found to promote Tau aggregate uptake into microglial cells, with different antibodies showing varying effects on aggregate size and epitope preferences. These findings suggest that antibody mechanisms include microglial clearance and inhibition of neuronal uptake, providing insights for optimizing therapeutic agents [20].

Therapeutic advances for neurological disorders are hindered by limited understanding and access to the human central nervous system. Induced pluripotent stem cells (iPSCs) and CRISPR-Cas9 technology enable the creation of disease models, such as for Alzheimer's and Parkinson's disease, facilitating research and therapy development. CRISPR-based tools, including CRISPRi and CRISPRa, enhance gene expression control, improving disease modeling and potential therapies. Although challenges remain, the combination of iPSCs and gene editing offers great promise for precision medicine and neurological disorder treatments [21]. Despite over 100 years of research, the causes of Alzheimer's disease (AD) remain unclear, and many disease-modifying drug trials have failed. Drug repurposing (DR) offers a more cost-effective approach, with about 30% of ongoing AD clinical trials exploring repurposed drugs targeting various pathways like anti-amyloid, anti-inflammatory, and neuroprotective methods. Drugs originally approved for other conditions, such as insulin and metformin, show potential benefits for AD. DR could significantly shift AD research and development by targeting specific disease mechanisms [22].

Genetics and Alzheimer's: The Basics

For some people, Alzheimer's runs in the family. In early-onset AD, which strikes before age 65, specific gene mutations (in APP, PSEN1, and PSEN2) act like inherited instructions that disrupt how the brain processes amyloid—a protein linked to AD's hallmark plaques. These mutations confirm the idea that amyloid buildup is a key driver of the disease. For the more common late-onset AD, a gene variant called APOE4 significantly raises the risk of developing the disease. Beyond APOE4, researchers have found about 30 other genetic markers, both common and rare, that also influence AD risk.

These genetic clues do more than explain why AD happens—they guide us toward precision medicine. By analyzing someone's DNA, doctors could predict their likelihood of developing AD, spot it before symptoms start, and design treatments that match their genetic profile. While today's medications only ease symptoms, this genetic approach could lead to drugs that slow or stop the disease altogether [23].

Smarter Drug Development with Genetics

Most AD drugs target three areas: the brain's chemical signaling (cholinergic system), amyloid buildup, or tau protein tangles. Drugs based on the amyloid hypothesis aim to reduce amyloid production, prevent it from clumping, or clear it from the brain. Meanwhile, early research on tau-based treatments, like vaccines tested in animals, suggests they could stop neurodegeneration and memory loss. But here's the catch: many drugs fail because they're given too late, after AD has already damaged the brain.

Genetics could change that. By testing for risk genes like APOE4, TOMM40, or mutations in APP, PSEN1, and PSEN2, researchers can identify people who are likely to benefit from specific drugs and start treatment earlier. This approach creates more targeted clinical trials, grouping patients with similar genetic profiles to test therapies that are more likely to work for them. It's like matching the right key to the right lock, increasing the odds of success [24].

Inflammation and Genetic Risk

Inflammation in the brain plays a big role in AD's progression, and genetics influences how intense that inflammation gets. Certain genes control proteins (like IL-1, IL-6, and TNF-α) that ramp up inflammation, while others (like IL-10)

calm it down. Variants in genes like Toll-like receptor 4, COX-2, and IL-1 can increase AD risk or cause it to start earlier. Other genetic differences affect enzymes (COX-1, COX-2, and 5-lipoxygenase) that fuel inflammation or tweak receptors involved in brain signaling and memory. Understanding these genetic links helps scientists design drugs that cool down harmful inflammation in a way that's tailored to a person's DNA. This could protect brain cells and slow memory decline, offering a more personalized path to better outcomes [25].

Early Action Through Genetic Insights

In 2018, researchers were testing 26 AD drugs in advanced trials, with 17 focused on changing the disease's course, mostly by targeting amyloid through immunotherapies, BACE1 inhibitors, or anti-clumping agents. Only one drug, TRx0237, targeted tau. Many drugs, like solanezumab, didn't work, likely because they were given too late in the disease. With 46.7 million Americans showing early, symptom-free AD signs in 2017, starting treatment early is critical.

Genetic testing, like checking for APOE4 or TOMM40, lets doctors identify high-risk individuals and enroll them in studies like TOMORROW or DIAN-TU, which aim to prevent or slow AD before it takes hold. By combining genetic data with details about a person's lifestyle, environment, and health history, doctors can create a treatment plan that's as unique as they are. This personalized approach could lead to earlier interventions and better results, giving people a fighting chance against Alzheimer's [26].

A Hopeful Future

The road to beating Alzheimer's is long, but genetics is lighting the way. By understanding each person's genetic risks, we can move toward a future where AD is caught early, treated effectively, and maybe even prevented. It's a deeply personal approach to a disease that affects millions, offering hope for better days ahead.

Catching Alzheimer's Early with Biomarkers

Imagine catching Alzheimer's before symptoms even start. Biomarkers—measurable signs of the disease—are making this possible. Tests like cerebrospinal fluid (CSF) analysis, which checks amyloid and tau levels, and brain scans like PET imaging can spot AD-related changes early. Blood tests, such as those measuring amyloid, tau, or neurofilament light, are also gaining ground, with over 1,400 studies identifying promising markers. These tools help doctors decide who needs treatment, what kind to use, and when to start, ensuring therapies match each person's unique biology [27].

For example, high levels of oxidative stress or inflammation, detected through specific biomarkers, can guide doctors to prescribe antioxidant or anti-inflammatory drugs. However, challenges remain: these tests are expensive, standardizing them is tricky, and AD progresses slowly, requiring long, costly studies to prove treatments work [28].

Imaging the Brain's Changes

Advanced brain imaging, like diffusion tensor imaging (DTI) and PET scans, offers a window into AD's impact. DTI reveals damage to the brain's white matter—its communication highways—by measuring water movement in areas like the hippocampus and frontal lobes. These changes appear not only in full-blown AD but also in mild cognitive impairment (MCI), hinting at early damage. PET scans, using tracers like florbetapir, highlight amyloid plaques or measure brain activity, while new tau-specific scans map tangles. Together, these tools improve early diagnosis, track disease progression, and check if treatments are working, paving the way for more precise care [29].

Personalized Care that Puts Patients First

No two people with Alzheimer's are the same, and new care models reflects that. Precision medicine uses genetic information, like the APOE4 gene (which raises AD risk) or MTHFR mutations (linked to cognitive decline), to create custom plans. For instance, APOE4 carriers might benefit from a Mediterranean diet or specific exercise routines, while MTHFR mutation carriers could take targeted B-vitamin supplements to lower risk. Trials like DIAN and A4 show how tailoring care to a person's genetics, lifestyle, and preferences can improve outcomes and quality of life [30]. These approaches also aim to make care fairer, ensuring everyone—regardless of income or location—has access to cutting-edge diagnostics and treatments. By combining genetics with lifestyle tweaks, doctors can offer hope through prevention and early action.

The Gut-Brain Connection: A New Frontier

Surprisingly, your gut might play a role in Alzheimer's. Research shows that an imbalanced gut microbiome (dysbiosis) can fuel amyloid buildup, inflammation, and memory decline. Scientists are exploring ways to restore gut health using probiotics (like Lactobacillus), prebiotics, or even fecal microbiota transplantation (FMT). Early studies, mostly in animals, suggest these could reduce brain damage and improve cognition, but human trials are needed to confirm what works. Understanding how gut bacteria influence the brain could lead to new, non-invasive treatments to slow or prevent AD [31].

Discussion

The escalating burden of Alzheimer's disease and other dementias underscores the urgent need for innovative approaches to diagnosis, treatment, and prevention. The doubling of the global mortality rate from 12.21 to 23.54 per 100,000 between 1990 and 2021, coupled with projections of 152.8 million cases by 2050, highlights the impact of aging

populations and rising risk factors like diabetes and hypertension. Low- and middle-income countries bear the brunt, with two-thirds of cases driven by rapid population growth, poverty, and limited healthcare access. Even high-income nations struggle due to socioeconomic disparities, emphasizing the need for equitable solutions.

Conclusion

Alzheimer's disease remains a formidable global challenge, but recent advances offer a path forward. Biomarker-guided diagnostics, genetic insights, and emerging gut-brain research are transforming how we detect, treat, and prevent AD. Personalized care, leveraging tools like polygenic risk scores and lifestyle interventions, empowers patients and families to act early. While challenges like cost, stigma, and ethical concerns persist, the integration of multi-modal strategies—combining genetics, biomarkers, imaging, and novel therapies—holds immense promise. By addressing inequities and fostering international collaboration, we can move toward a future where Alzheimer's is caught early, managed effectively, or even prevented, reducing its devastating toll and restoring hope for millions.

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