Nutritional Neurosciences

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Application of Artificial Intelligence in Neurological Disorders

Springer

Nutritional Neurosciences

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Preface

Immense Need for Artificial Intelligence Intended for Current and Future

Neuro-Healthcare

Artificial intelligence (AI) is the competence and proficiency of a computer or a robot (computer-controlled) to execute specific tasks generally coupled with intellectual and logical minds. AI is mainly associated with the capability to explain, reason, simplify, detect portending, and acquire comprehension from previous experience. Globally, AI has continually pertained to the undertaking of advancing systems conferred with the rational, analytical, and knowledgeable progressive features of human beings. Consequently, AI's impact on humanity is extensively discussed for its impact on the ability to considerably enhance the quality of human life by undertaking common, intricate, and complex jobs significantly better than a skilled person or a professional. Thus, AI can lead to a safe, more accessible, and competent lifestyle, resulting in decreased pathologies and improved healthcare worldwide.

As per the World Health Organization (WHO), neurological diseases and disorders are pathological ailments associated with the central (brain & spinal cord) and peripheral nervous system (somatic and autonomic). Neurological diseases can be generally classified based on structural (anatomical) and functional (physiological) aspects with the perspective of reversible or irreversible pathologies. Globally, billions of humans of different ages and sexes are diagnosed and drastically affected by various neurological disorders. The various reversible and irreversible neurological disorders have been shown to drastically upsurge morbidities and lead to faster mortality. Thus, neurological disorders affect the global economy, and therefore there is an imminent requirement for the use of technology to diagnose, prevent, and treat to improve healthcare significantly.

AI can play a decisive role in early diagnosis (genomics, proteomics, microarray data), synthetic/natural bioactive-based drug designing, and novel dosage pharmaceutical development for improved pharmacokinetic and pharmacodynamic effects with minimal adverse drug effects and hypersensitivity reactions. Further, large, complicated, and dense information acquired from human clinical trials poses a challenge to its implementation. However, AI, with its deep learning algorithms and simulated neural networks, has transformed the healthcare industry to progress and advance healthcare substantially.

Therefore, this book focuses on the role of AI in dementia (specifically Alzheimer's), neuronal cancer, cerebral disorders, depression, epilepsy, movement disorders, neuro-COVID, psychosis, and spinal cord injury.

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Mullaicharam Bhupathyraaj is a Professor of Pharmaceutics at the College of Pharmacy, National University of Science & Technology, Muscat, Sultanate of Oman. She has more than two decades of teaching and research experience and has received awards at the national and international levels. She received many research grants from HRD, AICTE, RG, and MoHERI (NRG, TRC), Oman, and has 6 international patents. Her research interests include, but are not limited to, biomedical, nanopharmaceuticals, herbal formulation development, and applications of AI. She has publications and patents in the field of artificial intelligence in medical imaging. She has published more than 100 research articles in peer-reviewed journals, written several book chapters, served as an editorial board member and reviewer for various peer-reviewed journals, and presented many papers at various conferences in India, the UK, Italy, the USA, Oman, and the UAE.

She has authored many textbooks (USA and Germany). She is an external examiner for Ph.D. theses of various universities and a reviewer of peer-reviewed journals. She is a Registered Pharmacist in India and a life member of professional bodies of IPA, APTI, IPGA, and ISTE. She organized many seminars and conferences. She is the external reviewer of the Oman Academic Accreditation Authority, Sultanate of Oman. She performed as an evaluator of international educational projects in the QS Reimagine Education Awards, UK, 2023. She is a Registered Pharmacist in India and a life member of professional bodies of India and Oman.

K. Reeta Vijayarani serves as the guiding light for the Pharmaceutics Department at Surya School of Pharmacy in Vikravandi, Villupuram. Prof. Vijayarani brings an enriched experience of nearly three decades in pharmaceutical education and research domain. Her academic journey is adorned with myriad contributions spanning across various national and global platforms. Her project total exceeds 60, ranging from research papers to enlightening posters and influential conference presentations. Prof. Vijayarani is a highly regarded author whose works have been

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Muralikrishnan Dhanasekaran is a Professor in the Department of Drug Discovery and Development at Harrison School of Pharmacy, Auburn University, USA. He has more than 110 peer-reviewed international publications, and several book chapters, and is a reviewer of various peer-reviewed journals. Prof. Dhanasekaran's lab and research interests are in preclinical research and drug development in neuropharmacology. His current research involves elucidating the neuroprotective and neurotoxic effects of natural bioactive and synthetic compounds and discovering and developing drugs/compounds targeting epilepsy, Alzheimer's disease, and Parkinson's disease.

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Chapter 1
Current and Futuristic Role of Artificial Intelligence for the Prevention and Treatment of Alzheimer's Diseases

Bennett Lange, Suhrud Pathak, K. Reeta Vijayarani, Jack Deruiter, Hanan Fahad Alharbi, Mullaicharam Bhupathyraaj, Kiruba Mohandoss, and Muralikrishnan Dhanasekaran

Abstract Dementia is described as an inherited neurological disease that causes a steady decline in intellectual performance, particularly with memory loss and difficulty thinking abstractly, as well as corresponding personality changes. Dementia in the form of Alzheimer's disease is by far the most common kind. Cholinergic neurons in the central nervous system are the target of Alzheimer's disease, a neurodegenerative condition. Dementia is currently the seventh leading cause of death and one of the major causes of disability and dependency among older people globally. Given its ubiquity, Alzheimer's disease is extremely disruptive on a mental, physical, and financial level. Alzheimer's disease has been challenging to diagnose, treat, and prevent up until recent years. A technique that has gained attention is artificial intelligence (AI), which has the potential to completely change how Alzheimer's disease is diagnosed, treated, and prevented. It is crucial to be able to

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make a diagnosis months or years before medical professionals are able to detect any physical changes. AI has the ability to alter the future of medicine completely. The use of AI in medicine is more significant than AI in general, like virtual assistants, in E-commerce, and in automobiles. AI will be a tool that reduces morbidity and death when used in conjunction with qualified medical professionals. This book addresses potential AI diagnostic, preventative, and therapeutic approaches.

Keywords Artificial intelligence · Dementia · Alzheimer's disease · Neurodegenerative · Acetylcholine (ACh) · Healthcare

1.1 Introduction

Dementia has been defined as an organic brain disease resulting in progressive loss of intellectual functioning, especially with impairment of memory and abstract thinking and associated changes in personality (*What Is Dementia?* 2023). Currently, over 55 million people have been diagnosed with dementia worldwide (*Dementia* 2023), including over 7 million people in the USA (*Fact Sheet: US Dementia Trends* 2021). With increases in life expectancy and aging of populations, the number of people with dementia is expected to grow. Dementia is a broad term, including many neurological diseases like Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, and mixed dementia. Of these, Alzheimer's disease is by far the most prevalent form of dementia, comprising an estimated 70% of all dementia cases, according to the Alzheimer's association (*What Is Dementia?* 2023).

1.2 Epidemiology

Alzheimer's disease affects an estimated 25 million people worldwide, and over 80% of Alzheimer's patients are over the age of 75 ("2020 Alzheimer's disease facts and figures" 2021). This demonstrates a clear association between the risk of disease and aging. Over time, reactive oxygen species will build up, and brain mass will decrease. This can already put them at risk of showing symptoms of Alzheimer's without actually having the disease by presenting loss in cognition and memory, but as the disease starts to develop, it can present its symptoms more boldly since the cognition and "shield" have already been removed by aging (Sengoku 2019). In fact, in February of 2023, the youngest person to date was diagnosed with Alzheimer's in China at 19 years old (Jia et al. 2023). As time passes, this problem will only get worse, though. As medicine improves, so does the average life expectancy, which means more and more of the population will reach the "high-risk" category and possibly develop the disease. In fact, it is estimated that by 2030, over

1 billion people will be above the age of 65, which is over 500 million more than it was in 2000 (Qiu et al. 2009) (Tables 1.1 and 1.2).

Significant data has shown that racial groups have differing rates of developing Alzheimer's. Among Americans, African Americans are the most likely to develop Alzheimer's disease (Matthews et al. 2019). However, this is not believed to be due to genomic differences between the races. Instead, it may result from the fact that stress as a child may age the brain faster, leading to higher rates of Alzheimer's as an adult (*Stressful Life Experiences Age the Brain by Four Years, African Americans Most at Risk* 2017). Stress can age the brain and put it at a higher risk of Alzheimer's in a few different ways, including increased cortisol levels and inflammation (Khalsa 2015). An elevated cortisol level over extended periods is neurotoxic, destroying hippocampal neurons (Khalsa 2015), which can initiate the onset of Alzheimer's. Similarly, inflammation due to stress can increase amyloid-β concentrations (Doig 2018), which can lead to the development of Alzheimer's (Doig 2018). This could explain why racial minorities tend to be affected by Alzheimer's the most and that this difference is a sociological difference and not a biological one, although more research must be done to establish this relationship. Sex-based differences in the incidence of Alzheimer's disease have also been proposed, but currently, this remains a disputed topic. A study in 2015 found that in America women were diagnosed with Alzheimer's at a higher frequency for every racial subgroup. It is believed that menopause, a midlife hormonal change unique to women, may play a role in the development of Alzheimer's (Scheyer et al. 2018) by uncoupling from the brain's bioenergetic system. This can lead to decreased metabolic activity and increased amyloid-β content. This has been confirmed through different tests when compared to other women who have not gone through menopause and other similarly aged men (Scheyer et al. 2018).

1.3 Symptoms of Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disease that targets cholinergic neurons (Ferreira-Vieira et al. 2016) in the brain. These neurons are present in the thalamus, limbic system, striatum, and neocortex, which suggests that they play a vital role in memory, learning, and movement, which, when in decline, are all common

Table 1.1 Percentages of age groups diagnosed with Alzheimer's by race in 2015 (Matthews et al. 2019)

	Aged 65–74 (%)	Aged 75–84 (%)	Aged 85+ (%)
African American	6.0	19.2	43.1
Hispanic	4.7	17.1	40.2
Non-Hispanic white	3.7	12.6	33.6
American Indian or Alaskan native	3.8	13.8	34.6
Asian and Pacific islander	2.8	11.7	32.2

Table 1.2 Percentages of gender groups diagnosed with Alzheimer's by race in 2015 (Matthews et al. 2019)

	Male (%)	Female (%)
African American	13.8	15.1
Hispanic	9.9	13.9
Non-Hispanic white	8.3	11.9
American Indian or Alaskan native	7.9	10.0
Asian and Pacific islander	7.0	9.5

Table 1.3 Common symptoms of Alzheimer's disease based on progression (*What Are the Signs of Alzheimer's Disease?* 2022)

Mild Alzheimer's symptoms	Moderate Alzheimer's symptoms	Severe Alzheimer's symptoms
Memory loss	Confusion	Inability to communicate with the caregiver or family members
Poor judgment	Withdrawal	Trouble swallowing and basic human functions
Poor problem-solving skills	Shortening of attention span	Grunting
Personality changes	Trouble recognizing relatives and friends	Seizures
Frequently getting lost	Trouble with daily repeatable tasks	Weight loss
Forgetting the date/day of the week	Paranoia	Loss of bowel and bladder control

symptoms of Alzheimer's disease (*What Are the Signs of Alzheimer's Disease?* 2022) (Table 1.3).

The complete list of symptoms is vast, and this table is by no means comprehensive. However, a general trend can be noticed. In mild Alzheimer's, cognitive dysfunction begins to play a role, and a general loss in memory, motor skills, and personality can be observed. In moderate Alzheimer's, a more distinct personality change is observed, and memory (trouble recognizing family and friends) begins to become greatly impaired. Finally, severe Alzheimer's sets in before death. This stage is characterized by an almost complete loss of personality, motor control, and memory (*What Are the Signs of Alzheimer's Disease?* 2022).

1.4 Causes of Alzheimer's Disease

Alzheimer's is believed to be caused by oxidative stress (Chen and Zhong 2014) and inflammation (Sinyor et al. 2020). There are two main pathologies associated with Alzheimer's disease: neurofibrillary tangles (NFTs) and senile plaques (Wooten et al. 2006). NFTs are a result of tau protein-related diseases (Laurent et al. 2018). Tau is a stabilizing protein that is associated with microtubules, or the skeleton, of

neurons; although they are found in trace amounts throughout the body, they are found on chromosome 17 and contain 16 exons. They play a role in stabilization, movement, transportation, and structure (Ye et al. 2022). To do many of these roles and to increase their functionality, tau protein is often phosphorylated in one or more of their 85 possible phosphorylation sites (Laurent et al. 2018) through acetylation, glycation, glycosylation, methylation, nitration, truncation, and ubiquitination (Laurent et al. 2018). These steps allow a phosphate group to be added to tau, which lowers its affinity for microtubules. Although this sounds counterproductive, it helps with axonal transport (Laurent et al. 2018). Two different enzymes regulate these processes (kinases for phosphorylation and phosphatases for phosphate hydrolysis). Under normal working conditions, these processes work in homeostasis, but tau protein-related diseases, due to inflammation and oxidative stress (Laurent et al. 2018), can lead to hyperphosphorylation. Hyperphosphorylation causes tau protein to lose its function and gain toxicity. The exact molecular reason for hyperphosphorylated tau toxicity is currently unknown, but it is known that it eventually begins to attract healthy tau (Gong and Iqbal 2008). When enough tau is surrounding the hyperphosphorylated tau, an NFT forms (Gong and Iqbal 2008). NFTs are pathogenic because of their ability to block neurons' transport systems, which can lead to the inability to communicate and access nutrients. This can lead to the rapid neurodegeneration that is the staple of Alzheimer's disease (*What Happens to the Brain in Alzheimer's Disease?* 2017).

Alongside NFTs, senile plaques are also believed to contribute as a precursor to Alzheimer's disease. Senile plaques are caused by an accumulation of amyloid-beta (Aβ) amino acid chains (Cras et al. 1991). Aβ is a byproduct of a large amyloid precursor protein, which is thought to be a cell surface receptor protein, although the exact use of the protein is unknown. Some possible functions of Aβ including antimicrobial activity, blocking leaks in the BBB, and recovery due to brain damage have all been proposed (Morley et al. 2019). The amyloid precursor protein gene is found on chromosome 21, with 18 exons (Zhang et al. 2012). Aβ, though, is formed through a long process. In this process, the amyloid precursor protein is first cut by β-secretase, then α-secretase to form a secondary amino acid chain, which is then further cut by γ-secretase to form either a 40- or 42-long amino acid chain (hence the name amyloid-β 40 and 42) (Rukmangadachar and Bollu 2022). These become beta-pleated sheets and form amyloid plaques, a staple in Alzheimer's disease, which increases both inflammation and oxidative stress in the brain, which can lead to an increase in hyperphosphorylation. Current research shows that these Aβ clumps inhibit cell-to-cell signaling ("Alzheimer's Changes the Whole Brain" 2023) as well as increase microglia neurotoxicity (Giulian et al. 1995), both leading to neuron death.

A recent study in 2018 (Doig 2018) has found that NFTs and hyperphosphorylated tau may be a result of an excess amyloid-β 40 and 42 (Aβ) feedback loop. As mentioned earlier, an increase in amyloid-β increases both oxidative stress and inflammation, which can increase hyperphosphorylated tau and NFT concentration. Both of these, though, can also act as a way to increase Aβ concentration. By increasing oxidative stress, low-density lipoprotein receptor-related protein 1 (a

protein used to move amyloid-β to the bloodstream and away from the brain) can become oxidized and lose its ability to remove Aβ (Doig 2018). This can lead to an overaccumulation of amyloid-β concentration. Similarly, through inflammation, Aβ is able to bind to endothelial cells and stimulate inflammatory cytokines. This increases COX-2 concentration, which leads to an increase in PGE2, PGD2, and γ-ketoaldehydes levuglandin E2 and LGD2 (Doig 2018). Both of these can prevent the proteolysis of Aβ. This inhibits the body from being able to regulate healthy levels of Aβ in the body and can lead to an overaccumulation of Aβ in the brain. Over time, this overaccumulation perpetuates the cycle going.

1.5 Diagnosis of Alzheimer's Disease

Post-mortem brain biopsies were done to confirm the existence of senile plaques, but such confirmation could not be done while the patient was alive (*How Is Alzheimer's Disease Diagnosed?* 2022). Instead, physicians have diagnosed the disease using clinical criteria and likely contributory risk factors. If the patient was elderly and had prolonged memory loss and cognitive decline, then they were more often than not diagnosed with Alzheimer's. However, physicians are now able to use many different biomarkers and brain imaging to confirm the suspicion of Alzheimer's. Amyloid-β 40 and 42 concentrations, as well as hyperphosphorylated tau, can both be measured in the cerebral spinal fluid through a painless lumbar puncture (Mantzavinos and Alexiou 2017). For Aβ, the cutoff limit has recently changed. Previously, a study had found that the minimum cutoff for Alzheimer's disease was 550 pg/mL. However, a recent study has shown that a new cutoff of 680 pg/mL should be used (Bertens et al. 2017). For tau concentration, it was found that an average of 26.06 pg/mL should be expected for healthy groups. In patients with Alzheimer's, however, they were found to have an average concentration of 36.41 pg/mL. Both of these studies were found to be statistically significant (Eckhoff et al. 2021). Also, recently, science has become much more adept at diagnosing Alzheimer's with brain imaging. Imaging alone, however, cannot be used to confirm a diagnosis of Alzheimer's (*Earlier Diagnosis* 2023). Using magnetic resonance imaging (MRI), multiple scans can be taken across time frames, and brain mass loss can be compared. Positron emission tomography (PET) scan also has been used, which is a scan that measures the decay of radioactive sugar (*PET Scan* 2023); by measuring the speed of decay, physicians are able to see which parts of the brain have increased/decreased metabolism. This can be used to see which parts of the brain's decay are actively affecting (*Earlier Diagnosis* 2023). Similarly, PET scans can also be used to detect the presence of both tau protein and Aβ concentration using molecular imaging (MI). MI is able to measure not glucose metabolization but instead radioactive "tags" that bind with specific amino acid chains (Rowe and Pomper 2022).

1.6 Treatment of Alzheimer's Disease

No matter how effective diagnosing Alzheimer's is, without treatment, the diagnosis would only establish a painful death sentence. There are multiple branches of research being done at the current moment for a cure, including targeting amyloid-β concentration, tau protein concentration, acetylcholinesterase inhibition, and gene therapy. All of these, though, have yet to prove highly effective. They are, though, promising and have shown the ability to either diminish symptoms or slow down neuronal death. The first of the newer family of medications targets amyloid-β concentration. As mentioned earlier, Aβ either encourages or is the main cause of both possible causes of Alzheimer's. This means that stopping Aβ from forming could be a major step toward ending Alzheimer's. A monoclonal antibody medication named aducanumab was approved by the Food and Drug Administration (FDA) in 2021 ("Aducanumab Approved for Treatment of Alzheimer's Disease"). This drug is a human immunoglobulin gamma 1 monoclonal antibody and targets the third through seventh amino acid on Aβ (Padda and Parmar 2023), which is administered intravenously in a single-use manner. While not a permanent cure, it does, however, appear to slow down senile plaque formation. This should extend the life expectancy for patients, as well as increase their remaining quality of life by decreasing their cognitive decline ("Aducanumab Approved for Treatment of Alzheimer's Disease"). In trials to date, aducanumab patients were found to have a longer life expectancy of 2.58 years (Herring et al. 2021) and showed improvement in a clinical dementia test score (22%) as well as decreased their cognitive decline by 40% when compared to the placebo group (Beshir et al. 2022) (Table 1.4).

This drug was fairly controversial when released, though, due to its very high rate of significant adverse side effects and lingering questions about its efficacy. Over 35% of treated patients experienced cerebral edema, 19% experienced microhemorrhages, and 21% experienced trouble with balance, etc. (Padda and Parmar 2023). Thus, patients will have to decide if the increased years of quality of life and cognitive function are worth the high chances of adverse side effects, which is a decision that also impacts the caregivers since many Alzheimer's patients do not have the mental capacity to make these types of decisions on their own, this burden will often fall on the caregivers to make the decision for the patient. Second, the

Table 1.4 Common adverse side effects and rates of aducanumab (Padda and Parmar 2023)

Edema	35%
Microhemorrhage	19%
Superficial siderosis	15%
Headache	21%
Increased risk of falling	15%
Diarrhea	9%
General disorientation	8%
Hypersensitivity	<1%
Immunogenicity	<1%

effectiveness of aducanumab has also been under scrutiny. Although its studies have shown statistically significant increases in lifespan, the Peripheral and Central Nervous System Drugs Advisory Committee voted 10–1 that it did not meet the criteria to be considered more effective than the placebo (Tampi et al. 2021). Also, the high cost ($56,000 annual cost), uncertainty (post-approval confirmatory trial will not be finished until 2030), and the fact that many trial patients have left other drug trials to take aducanumab have all contributed to the uncertainty of this drug (Tampi et al. 2021).

It was mentioned earlier that Alzheimer's affects cholinergic neurons in the brain, but a more in-depth approach is necessary to understand medicine that targets acetylcholinesterase inhibition. In Alzheimer's, cholinergic neurons begin to die rapidly (Ferreira-Vieira et al. 2016), eventually resulting in the loss of over 80% of all cholinergic nerves. These neurons are necessary to the brain's ability for neuronal excitability, synaptic transmission, synaptic plasticity, and coordinating the firing of groups of neurons (Picciotto et al. 2012). After neuron death, though, the amount of the cholinergic neurotransmitter acetylcholine in the brain greatly decreases, which leads to an inability for synapses to fire and an inability of neuronal communication and leads to the progression of dementia, cognitive decline, memory loss, and brain matter loss (Ferreira-Vieira et al. 2016). To combat this loss, it would be attractive to administer an excess amount of acetylcholine. Unfortunately, acetylcholinesterase, an enzyme responsible for the breakdown of acetylcholine, and other esterases in the body are far too efficient and make delivery of acetylcholine impractical. A single acetylcholinesterase has been found to break down over 600,000 molecules of acetylcholine (Byrne 2023). Alternatively, an acetylcholinesterase inhibitor could enhance existing concentrations of acetylcholine in the CNS by slowing its metabolic breakdown. Donepezil, an acetylcholinesterase inhibitor, has been an FDA-approved drug since 2004. It is given orally in doses of 5, 10, and 23 mg/day, depending on the severity of Alzheimer's progression, and while this drug has been shown to slow cognitive decline, it does not appear to extend the lifespan of Alzheimer's patients (Kumar et al. 2023). In a recent study, donepezil was found to promote a statistically significant decrease in cognitive decline in a 6-week study of 5 mg/day, a 12-week study of 5–10 mg/day, and an 18-week study of 10 mg/day. After 24 weeks of 10 mg/day, a significant increase in both the Mini-Mental State Exam and the Alzheimer's Disease Assessment Scale was found in treated patients (Knowles 2006). This decrease in cognitive decline was found to persist for up to and slightly beyond 52 weeks; however, after this time-period the decrease slowly began to disappear, an apparent shortcoming of donepezil. But donepezil, unlike aducanumab, has much lower adverse side effects, with its most prevalent adverse side effect (nausea) occurring at a rate of 5% of all patients (Kumar et al. 2023).

Another approach to the treatment of Alzheimer's involves the development of tau protein antibodies. This approach, unlike aducanumab and donepezil, has yet to yield a medication approved by the FDA. Despite anti-tau medications being at the forefront of research for the last 25 years, there have been minimal results. Those still researching tau toxicity are similar to aducanumab, hoping that this may

completely or severely hinder Alzheimer's ability to advance throughout the brain by using anti-tau monoclonal antibodies. In 2020, there were only four anti-tau monoclonal medications under consideration in the FDA approval process. The first, gosuranemab, was discontinued in 2021 after showing no superiority in clinical outcomes when compared to the placebo. The second, tilavonemab, was discontinued after performing worse than the placebo. Zagotenemab, despite showing improvement, was discontinued after AbbVie announced it had yet to meet the endpoint they had projected. Currently, only semorinemab remains in the approval process, and it is waiting on phase three approval from the FDA (Teng et al. 2022).

The final main treatment being researched is gene therapy. Gene therapy is defined as any treatment that includes nucleic acid, and its diagnostic, prophylactic, or therapeutic abilities mainly revolve around the nucleic acid of cells. Currently, there are two types of gene therapy: germ-line therapy (genetic editing that can be passed on to the next generation) and somatic gene therapy (genetic editing that cannot be passed on to the next generation). Since germ-line therapy is currently illegal, only somatic gene therapy can be accessed to treat Alzheimer's. Gene therapy utilizes viruses to inject cells with suspected genetic defects with a corrective gene product. These genetically modified viruses are able to inject a "fixed" human genome into an existing cell, changing its DNA (*Gene Therapy for APOE4 Homozygote of Alzheimer's Disease* 2018). This was obviously a breakthrough in the medical field. The main gene currently being researched is the APOE2, APOE3, and APOE4 gene (Khan et al. 2020). In recent studies, it has been found that humans with one copy of the APOE4 gene are 6 times more likely to develop Alzheimer's, and if they have 2 copies, that chance goes to 12 times more likely (Khan et al. 2020). APOE3 is considered to be the baseline, while APOE2 has been found to reduce the likelihood of developing Alzheimer's. Recent trials have been promising. In one study, five patients with two copies of the APOE4 gene were given a low dosage of gene therapy and Aβ and tau levels both decreased in their spine. This was exciting enough that trials have moved on to a higher dosage, but data has yet to be released at the most recent date of writing (September 2023) (*Gene Therapy for APOE4 Homozygote of Alzheimer's Disease* 2018). In another study, it was found that all three trials upregulated neuronal growth factor (NGF) (Lennon et al. 2021), which is a protein that has been found to influence cholinergic neurons (Jia et al. 2018). Although promising, there are still several issues with gene therapy that must be addressed, including the difficulty of understanding the human genome for polygenic diseases, the discomforts many patients will feel with the delivery method (intracranial injection and lumbar punctures), and even the discomfort many patients will feel regarding gene therapy's morality.

1.7 Prevention of Alzheimer's

Since Alzheimer's is currently incurable, prevention may represent an attractive alternative. If methods were developed to stop the pathologic process of Alzheimer's, the fact that it is always lethal would become inconsequential. There are two main ways that Alzheimer's can be prevented. First off is lifestyle changes. In a Swedish study, it was found that people who spend their lives building and utilizing cognitive skills were 46% less likely to develop Alzheimer's (Qiu et al. 2009). Similarly, bilinguals were found to develop the disease significantly later than monolinguals (Zheng et al. 2018). It is believed that constant cognition and engagement build a cognitive and brain mass wall. This allows symptoms of Alzheimer's to present themselves later in the patients' lives (Qiu et al. 2009). The reverse has also been found to be true. Patients diagnosed with depression have been found to be at a higher risk of developing and showing symptoms of Alzheimer's later in life. However, there are multiple possible causes for this, including depression being found to induce oxidative stress and inflammation, so more research needs to determine if there is a relationship between these diseases (Qiu et al. 2009). Like these risk factors, obesity, diabetes, hypertension, dyslipidemia, and traumatic brain injuries were all found to increase the chance of a person developing Alzheimer's. All of these findings taken together suggest that one way to prevent Alzheimer's is to adopt a healthy and intellectually active lifestyle. By exercising both the body and mind, as well as a good diet, there could be a significant decrease in the chance of developing Alzheimer's disease.

Another preventative measure for Alzheimer's may be prophylactic medication. In one study, it was found that nonsteroidal anti-inflammatories were able to decrease the chance of developing Alzheimer's by decreasing inflammation in the brain and spine (Zhang et al. 2018). However, it was also found that consistent, low-dosage aspirin does not affect the chance of developing Alzheimer's. At present, more research remains to be done to evaluate the therapeutic potential of medications. Also, it is now recommended not to overuse anticholinergic medication (tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics were the tested drugs) (*Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices* 2022). It has been found that an increased use of these classes of drugs is associated with a rise in dementia due to the long-time decrease in cholinergic neurotransmission (*Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices* 2022).

1.8 Need for Artificial Intelligence in Medicine and Neuroscience

With its prevalence, Alzheimer's is a tremendous cost mentally, physically, and financially. In one study, it was found that per-patient cost in the USA was over 19,000 dollars a year and that the whole country spent over 165 billion dollars on care in 2015. It is estimated that the country will spend over two trillion dollars on care in 2030 and over nine trillion by 2050 (Jia et al. 2018). Lowering the cost, mortality, and morbidity is paramount globally. Artificial intelligence (AI) is a tool that has come under the spotlight with the potential to revolutionize the diagnosis, treatment, and prevention of Alzheimer's. Artificial intelligence (AI) has recently exploded across news sites, going from a poorly designed chatbot to a tool capable of passing a bar exam (Ahn 2023) in just a few years. More important than writing AI, though, is the application of AI for medical purposes. The importance of being able to diagnose months to years before doctors would be able to notice any bodily change could not be understated.

Although AI could represent a valuable tool in the future and even the present day for the diagnosis and treatment of disease, it must be stated that it can be assumed that AI will never completely replace physicians in the current generation's lifespan. The ability of physicians to provide hospitable, accurate, and personalized treatment plans for patients is vital to the diagnostic and healing process. Not every person can be treated using AI software. AI can, though, act as a second opinion or confirmatory device that will assist future physicians. AI can currently diagnose patients years before doctors know what they are looking for in many cases (to be discussed later). This allows for multiple possibilities: earlier treatment, mental preparation and acceptance, and saved money.

Earlier treatment will likely be the most important facet of AI. Almost every person knows someone who says something along the lines of "I am just glad we caught it so early" or "If only we had caught it earlier, we could have started treatment." With disease and cancer, the ability to treat earlier can dramatically decrease the progress of the disease and decrease mortality and morbidity. Rheumatoid arthritis (RA) is an example of this. In one study, patients were diagnosed 2 years prior to symptoms of RA becoming present and were treated with either three disease-modifying antirheumatics drugs (DMARDs) or one DMARD (Table 1.5).

Both treatment groups had an increased rate of remission due to the early diagnosis (Heidari 2011). This approach can also be applied to different cancers. According to the American Cancer Society, in non-small cell lung cancer, if it is diagnosed in stage I or II and treatment is done, the 5-year survival rate is 61%,

Table 1.5 Remission rate of rheumatoid arthritis due to early diagnosis

	Remission rate after 2 years (%)	Remission rate after 5 years (%)
3 DMARDs	40	28
1 DMARD	18	22

whereas stages III and IV are only 24% (*Treating Non-Small Cell Lung Cancer* 2023). This trend also follows in the stomach (*Stomach Cancer* 2023) and pancreatic cancer (*Pancreatic Cancer* 2023). AI will aid in physicians' ability to use imaging, biomarkers, and symptoms to accurately diagnose diseases and cancers years before they would normally be able to notice them, which will help us accurately and effectively treat all kinds of ailments. This will decrease morbidity and mortality and enhance the opportunity to effective medical intervention.

The second way that AI can act as a tool will be by allowing patients to mentally prepare and accept outcomes. This is a much sadder and more abstract concept than early diagnoses and treatment but still a necessary one. Currently, in certain diseases like Alzheimer's or Huntington's Disease, there is no cure, and a diagnosis will likely be a promise for early mortality. However, this does not mean that a diagnosis will always be useless. In certain cases, like Alzheimer's, mental decline is inevitable, and the patient will eventually not be of sound mind to make their own medication and treatment decisions. However, an early diagnosis will allow them to make these choices beforehand, which can reduce the stress for caregivers and loved ones. This will also allow them to feel more in control of the disease since they are able to make their own decisions beforehand and allow patients to settle any financial issues before it becomes too late. Finally, it can allow them to resolve personal conflicts with family or friends they may have later wished to amend. Although an early diagnosis due to Alzheimer's may seem like a death sentence, it can also provide closure, a sense of power, and the ability to cross off any personal needs before it is too late.

The final way that AI can help in the management of disease is through the easing of treatment costs. In one study in 2016, an average cost of different stages of breast cancer treatment for patients from diagnosis to 24 months was found, and as the disease progressed, the cost did as well (Blumen et al. 2016) (Table 1.6).

As can be seen, by decreasing the stage of diagnosis, the cost of treatment for the patient can be greatly reduced by decreasing the amount of chemotherapy, the length required for remission with chemotherapy, and the decreased chance of requiring surgery. In a financial study using the numbers in the last study, they found that if all diagnoses cases were in stage 0/I, the cancer industry alone could save up to 26 billion dollars (Blumen et al. 2016). This could drastically reduce the financial hardships imposed on patients associated with the different medications and surgeries they may require. AI, if used correctly, can significantly decrease morbidity, mortality, and cost of treatment in treatable cases. In cases that cannot be cured, AI

Table 1.6 Average cost of breast cancer treatment by stage (Blumen et al. 2016)

Stage	Number of patients	Average cost
0	2300	$74,160
I/II	4425	$100,635
III	1134	$165,188
IV	501	$204,146

can still be helpful by providing patients the ability to choose their own treatment plans and rectify anything they cannot do after their disease progresses.

1.9 Basic Artificial Intelligence Knowledge

Before AI's influence on medicine can be discussed, general knowledge about the nature and potential of AI must first be established. Since AI has become so fascinating to so many people recently, it is easy to be persuaded by sensationalist headlines put out in the media. AI is not a Terminator-like killer with a will to take over the world, but AI's risks should not be underestimated either, for there are risks and obstacles inherent in its use. Generally, AI is a very broad term that can be defined as the theory and development of computer systems able to perform tasks that normally require human intelligence, according to Oxford Languages ("Artificial Intelligence"). This means that anything from a simple chatbot like Apple's Siri or Amazon's Alexa to self-driving cars is all under the broad AI umbrella. There are, though, different terminologies that are used to categorize AIs into more accurate groupings. The two main types of learning that AI will use in the medical field are machine learning and deep learning (Russell and Norvig 2022). Machine learning is programming that uses neural networks and defined laws that a programmer programs into the algorithm to make predictions. Machine learning is special; instead of using a flow chart of laws, it uses an immense amount of data to draw conclusions. Like humans, it is able to make predictions, similar to a hypothesis, based on the enormous amount of data available to it. Machine learning shows extreme promise in diagnosis situations (Rajkomar et al. 2019). Similar to how machine learning is a smaller subsection of AI, deep learning is a smaller subsection of machine learning (Fig. 1.1).

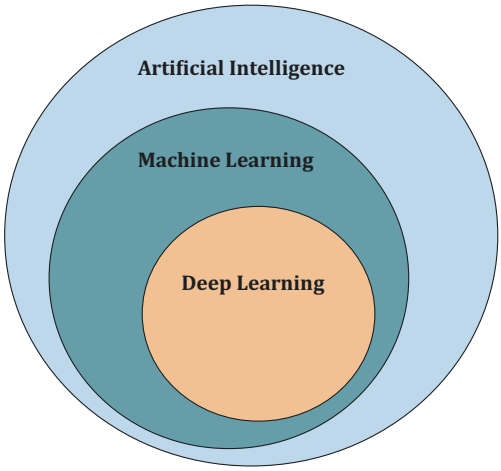

Fig. 1.1 A grouping of artificial intelligence, machine learning, and deep learning