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Advances in Computational Biology for Diagnosing Neurodegenerative Diseases: A Comprehensive Review

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Abstract The numerous and varied forms of neurodegenerative illnesses provide a considerable challenge to contemporary healthcare. The emergence of artificial intelligence has fundamentally changed the diagnostic picture by providing effective and early means of identifying these crippling illnesses. As a subset of computational intelligence, machine-learning algorithms have become very effective tools for the analysis of large datasets that include genetic, imaging, and clinical data. Moreover, multi-modal data integration, which includes information from brain imaging (MRI, PET scans), genetic profiles, and clinical evaluations, is made easier by computational intelligence. A thorough knowledge of the course of the illness is made possible by this consolidative method, which also facilitates the creation of predictive models for early medical evaluation and outcome prediction. Furthermore, there has been a great deal of promise shown by the use of artificial intelligence to neuroimaging analysis. Sophisticated image processing methods combined with machine learning algorithms

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make it possible to identify functional and structural anomalies in the brain, which often act as early indicators of neurodegenerative diseases. This chapter examines how computational intelligence plays a critical role in improving the diagnosis of neurodegenerative diseases such as Parkinson's, Alzheimer's, etc. To sum up, computational intelligence provides a revolutionary approach for improving the identification of neurodegenerative illnesses. In the battle against these difficult disorders, embracing and improving these computational techniques will surely pave the path for more individualized therapy and more therapies that are successful.

Keywords Neurodegenerative Disorders, Computational Biology, Technology

1. Introduction

1.1 Overview of Neurodegenerative Disorders

A vast range of illnesses affecting the nerve system is collectively referred to as neurological disorders, and they severely diminish the quality of life for millions of people globally. Neurons in the brain's central nervous system (CNS) or peripheral nervous system (PNS) continue to degenerate because of these illnesses. Important communication routes are disrupted by the decline of neuronal networks and the restricted ability of neurons to renew efficiently due to their permanently specialized state. In the end, this leads to problems with motivation, behavior, sensory perception, memory, and/or cognition (Wilson et al., 2023). A number of conditions are included in the category of neurodegenerative diseases, including frontotemporal dementia, Alzheimer's disease, Parkinson's disease, ALS, and spino cerebellar ataxias. These conditions show a variety of pathophysiological traits; some cause memory and rational issues, while others affect a person's ability to speak, move, and breathe (Abeliovich & Gitler, 2016; Taylor, Brown Jr, & Cleveland, 2016; Wyss-Coray, 2016; Gitler, Dhillon, & Shorter, 2017). Several common neurodegenerative diseases include:

1.1.1 Alzheimer's Disease (AD)

The primary cause of dementia, Alzheimer's is one of the most expensive, deadly, and debilitating illnesses in modern society.(Badun, 2019) (Miller, Bintener, and Georges, 2020). Dementia is another word for Alzheimer's disease, which bears Alois Alzheimer's name. Neuritic plaques and neurofibrillary tangles are the ultimate manifestation of this slowly progressing neurodegenerative disorder. (Figure 1). Plaques and tangles form in the brain's neocortical sections and medial temporal lobe due to the accumulation of amyloid-beta peptide (Aβ). The symptoms of the illness are more likely to affect these specific brain regions.(2012) De-Paula, Radanovic, and Diniz. Now over 50 million people worldwide have been diagnosed with Alzheimer's disease (AD). Based on this estimate, the population is predicted to rise exponentially, doubling every five years, and reach 152 million by 2050. As of right now, there is no known cure for Alzheimer's disease, yet there are treatments available that may totally improve symptoms (Breijyeh & Karaman, 2020; Livingston et al., 2020; Yiannopoulou & Papageorgiou, 2020). Alzheimer's disease (AD) exhibits two distinct forms of neuropathological changes that provide information on the illness's course and symptoms. The classifications include neurofibrillary tangle accumulation, amyloid plaque accumulation, dystrophic neurites, neuropil threads, and other lesions that are discernible in the minds of individuals afflicted with Alzheimer's disease.

Furthermore, doublet unfavorable lesions have been significantly reduced due to degradation of the neurons, synapses, and neuropils. Moreover, oxidative stress, neuroinflammation, and damage to cholinergic neurons are additional causes of neurodegeneratio n.(Singh, Srivastav, Yadav, Srikrishna, & Perry, 2016) (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011) (Spires-Jones & Hyman, 2014).

1.1.2 Parkinson's Disease (PD)

Parkinson's disease has a big social effect. Globally, the condition affected around 6.1 million people in 2016, demonstrating the disease's high prevalence (V. Feigin et al., 2019; V. L. Feigin et al., 2019). Over time, people with this illness often have mild disability and worsening. Given that it takes an average of ten years from the onset of symptoms to diagnosis, an early identification of Parkinson's disease may prevent consequences (Gaenslen, Swid, Liepelt-Scarfone, Godau, & Berg, 2011). Constipation, playing out dreams during REM sleep, hyposmia, an asymmetric generic shoulder discomfort, or depression are examples of early symptoms (Armstrong & Okun, 2020).

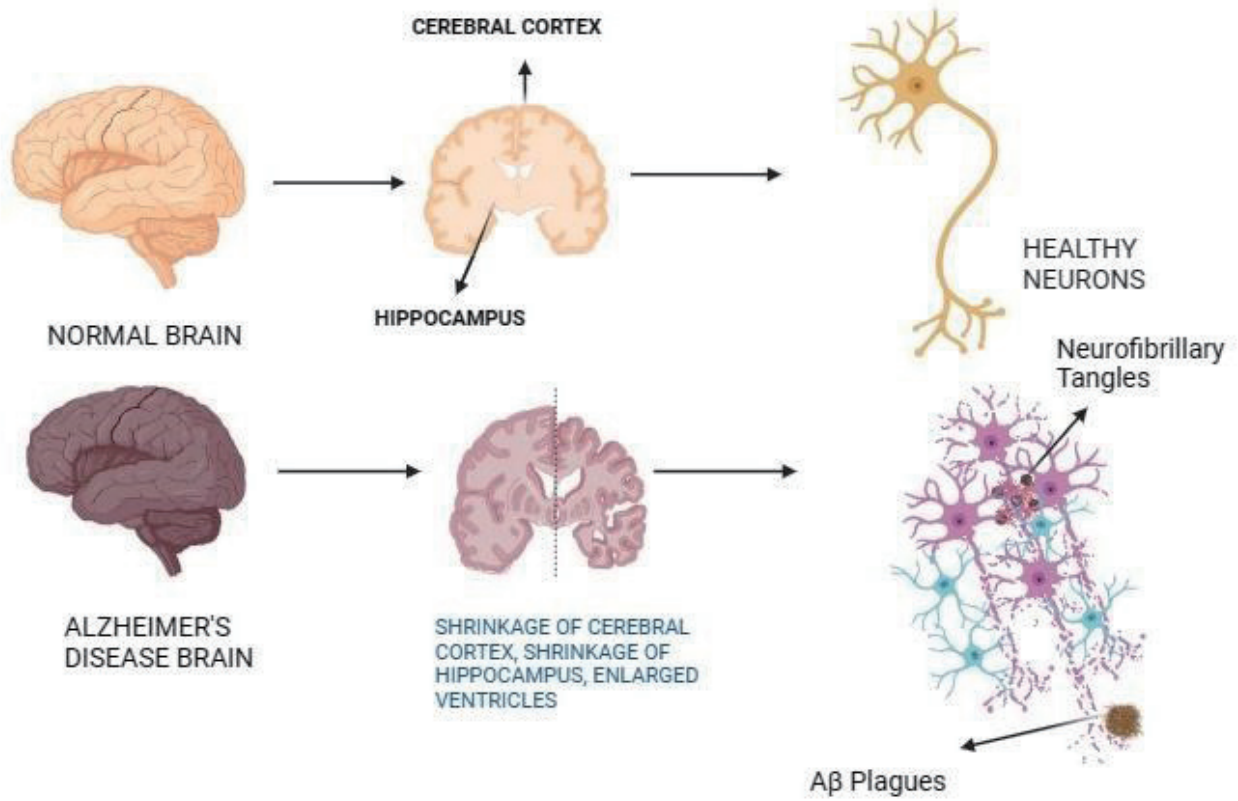

Figure 1: Diagrammatic Representation of Healthy Brain and Alzheimer's Brain

Parkinson's disease is an illness that increases in frequency with age, with an increase in instances as individuals become older. That doesn't mean, however, that it just affects the elderly. 5–10% of people affected are under 50 years old, while around 25% of those affected are under 65 (Pringsheim, Jette, Frolkis, & Steeves, 2014). Three factors may contribute to Parkinson's disease: environment, genetics, and their interactions. Investigations on gene mutations such as LRRK2, PRKN, SNCA, GBA, and PINK1 were still underway. According to Trinh et al. (2018), SNCA mutations are characterized by an early onset of disease, a fast progression of motor symptoms, and significant non-motor features such a quick decline in cognitive function. There are seven distinct LRRK2 mutations linked to Parkinson's disease. The main etiological factors responsible for autosomal recessive and early-onset Parkinson's disease have been identified as mutations in PRKN and PINK1. According to Kasten et al. (2018), PRKN mutations are associated with 77% of cases comparable to juvenile Parkinson's disease (onset age < 20 years) and 10–20% of cases of juvenile Parkinson's disease beginning (Bloem, Okun, & Klein, 2021).

1.1.3 Amyotrophic Lateral Sclerosis (ALS)

The neurodegenerative disease known as amyotrophic lateral sclerosis (ALS) affects both the top and bottom motor neurons, resulting in symptoms that are extra-motor as well as motor. Patients with ALS may exhibit symptoms of bulbar-onset illness, which results in swallowing and speaking problems, or spinal-onset disease, which causes muscular atrophy in the limbs. Most of the time, the cause of ALS is unknown. On the other hand, a small percentage of individuals with a family history have this illness, which is associated with genetic defects affecting several functions, including non-motor cells. The accumulation of ubiquitylated proteinaceous inclusions in motor neurons is a hallmark of ALS, albeit the underlying pathogenesis is yet unknown. Axonal loss, glial cell changes, and myelin pallor are seen in the corticospinal pathways, whereas astrocytic gliosis and variable reduction of higher motor neurons are usually observed in the motor cortex. According to Kiernan et al. (2011), skeletal muscle displays both degenerative change and reinnervation, as well as clustering and clusters of angular atrophic fibers, depending on the kind of fiber (Singh, G., et al, 2024)

1.1.4 Depression

A number of symptoms, including low self-esteem,

lack of desire, anhedonia, low appetite, low energy, and pain, are present in depression, a crippling illness that has no obvious cause. Some research indicates that maladaptive changes in certain brain circuits may be the cause of depression. It is now recognized that the lateral habenula (LHb) has a role in the pathophysiology of depression by influencing cognitive responses. The monoaminergic systems in the mesencephalon (midbrain) and rhombencephalon (hindbrain) are connected to the prosencephalon (forebrain) by the pristine structure known as the lateral habenula (LHb) (Aizawa, Amo, & Okamoto, 2011). The lateral habenula generates mesencephalon (midbrain) aminergic centers, including the GABAergic rostromedial tegmental nucleus (RMTg, also known as tail-VTA), serotonergic (5-HT) dorsal and median raphe (DRN, MRN), and dopaminergic (DA) substantia nigra pars compacta (SNc) and lateral habenula. According to Yang, Wang, Hu, and Hu (2018), the "amine theory of depression" suggests that a specific deficiency in monoamine neurotransmitters is the root cause of depression.

1.1.5 Dementia

Around the globe, dementia is linked to age-related impairment. Approximately 50 million people worldwide suffer from dementia, and 10 million new cases are identified year. When mental functions including memory, logic, and thinking deteriorate to the point that they interfere with day-to-day activities, dementia results. Individuals with dementia may go through emotional upheavals and personality changes. Memory loss, difficulty completing activities, confusion, language problems, behavioral abnormalities, and lack of initiative are some of the symptoms associated with dementia. Three stages were used to categorize dementia symptoms: early, middle, and late. Because 226 disorders progress gradually, it is difficult to discover them early. Time loss, amnesia, and trouble orienting in private settings are all symptoms of this illness (Singh S, et al, 2024). Events and identities alter more noticeably during the intermediate period. Additional symptoms include a higher need for personal cleanliness and communication problems. Wandering and inquiring for extended periods of time may cause behavioral changes. Uncommon symptoms in the latter stages include near-total reliance and inactivity due to memory problems. Walking difficulties, behavioral changes, trouble recognizing time and location, and trouble recognizing family and friends are some of the symptoms and indicators.

1.2 Need for Advanced Diagnostic Approaches

Conventional health technology assessment (HTA) makes conclusions on the clinical efficacy, safety, cost-effectiveness, and financial impact of medicines using a framework based on data modeling and evidence synthesis. The main drawback or limitation of previously used methods was their inability to identify the precise gene causing an issue and their inability to consistently establish the presence of a particular disease. The mammalian brain is a marvel of evolution, with well-organized chemistry, distinct cell architecture, and well-organized neuronal pathways in every cycle. In every instance, these attributes were related at the anatomical and practical levels (Borrell & Calegari, 2014). In this part, computational techniques for comprehending gene expression, brain function, and brain development/disease are discussed and brain transcriptome atlases are introduced. The rapid advancement of high-throughput technology has made it possible to measure millions of genes' reflections simultaneously. The transcriptome of the brain at various stages of development may now be examined thanks to next-generation technology. Atlases of the brain transcriptome provide essential information on the molecular makeup of the brain. Decoding high-dimensional transcriptome data requires computational methods. Researchers may examine the relationship between gene expression, anatomical characteristics of the brain, and neurological disorders by using transcriptome data and appropriate methodology. novel computational methods are required to uncover novel chemical underpinnings of the brain in order to solve limitations such as restricted decision-making and inadequacy of non-coding genes (Li & Wang, 2019).

2. Basics of Computational Biology

Computational biology is an interdisciplinary discipline that applies analytics, computer science, and mathematical applications to biological problems. Similar to other interdisciplinary fields, it applies the same computational and mathematical sciences to decision-making problems. Both concentrate on building mathematical models and coming up with solutions. The biological domains of computational biology models range from organism-species relationships to gene-protein interactions (Chicco, 2017). By characterizing ligand-binding mechanisms, locating active spots, and fine-tuning the structure of ligand-target binding poses, computational biology advances the field of drug development. Systems biology, which aims to comprehend how

biological systems work as a whole rather than as separate components, is another important area of computational biology. Systems biology builds models of biological systems, from metabolic networks to signaling pathways, and simulates their behavior under different conditions using experimental and computational techniques. Applications of systems biology include synthetic biology, personalized medicine, and drug discovery.

Computational biology is beginning to recognize the importance of machine learning. Massive biological datasets may be used to train machine learning algorithms to identify patterns, predict events, and gain new insights. Machine learning algorithms, for instance, have been used to assess the structure and function of proteins, find mutations that cause illness, and classify cancer subtypes according to patterns of gene expression. Novel drugs and treatments have also been developed because of computational biology. Virtual screening has become a standard strategy in drug research, using computer methods to find potential drug candidates from massive databases of chemicals. Additionally, computer simulations may be utilized to design new medications with better properties and predict the safety and effectiveness of treatments.

3. Applications of Computational Biology in Neurodegenerative Disorder Diagnosis

Approximately 40 million people worldwide suffer from neurodegenerative diseases (NDs). Because it is difficult to identify the many and varied pathophysiological processes that occur simultaneously in most of these disorders, there are often no effective therapies available to slow down or stop the progression of the disease. With the use of modern technology and computational abilities, there is hope for dissecting these changes and discovering novel pathways responsible for the onset and development of neurodegenerative disorders. In particular, integrating computational systems biology techniques with sophisticated omic analytical methods like mass spectrometry and microarray provides a methodical framework for identifying new pathways that underpin neurodegenerative illnesses. Factors like sample size, measurement number, previous biological knowledge, and hypothesis/question influence the computational analysis of multivariate data. Very little study has been done on using systems analysis methods with non-diagonal variables. The organized computational methods of systems biology may assist in elucidating the underlying mechanisms of several simultaneously occurring components of ND pathophysiology. The limitations of models in correctly representing human disease at the systems level may be brought to light by combining human tissue analysis with mice and culture models. At the system level, disease-causing pathways and processes may be identified by integrating perturbation and time point analysis into models. Even with different APs, the pathophysiologic presentation of NDs is similar.

3.1 Image and Computational Techniques

Cerebrospinal fluid (CSF) analysis, serum or urine tests, imaging, and electrodiagnosis are a few examples of further testing that may be required to confirm or rule out a neurologic diagnosis. To identify CNS disorders, imaging and electrodiagnostic techniques such as evoked potentials and electroencephalograms are often used. Over the last ten years, advances in technology have improved the analysis of the nervous system. Technological developments in magnetic resonance imaging (MRI), including high-resolution imaging and functional MRI (fMRI), have improved the ability to identify disorders of the central nervous system. Real-time diagnostic data for neurodegenerative disorders may be obtained via wearable technology and upcoming digital sensors (National Academies of Sciences & Medicine, 2023).

3.1.1 Neuroimaging Technologies

3.1.1.1 Magnetic Resonance Imaging (MRI)

When paired with modern methods, Magnetic Resonance Imaging (MRI) can evaluate blood circulation, detect iron accumulations, and give thorough neuroimaging of the brain and spinal cord. For the diagnosis of stroke, traumatic brain injury, brain and spinal cord tumors, inflammation, infection, vascular irregularities, brain damage related to epilepsy, abnormally developed brain regions, and some neurodegenerative disorders, the National Institute of Neurological Disorders and Stroke recommends using magnetic resonance imaging (MRI). The development of innovative diagnostic techniques has benefited greatly from the use of MRI technology and its integration with other diagnostic procedures throughout the last 30 years. When it comes to the diagnosis of multiple sclerosis, MRI is a crucial tool. An evoked potential test, MRI, or lumbar puncture are often preceded by a medical history and physical examination by clinicians in order to identify multiple sclerosis. Table No. 1 displays applications of magnetic resonance imaging in neurological diagnostics.

Table 1: Applications of Magnetic Resonance Imaging in Neurological Diagnostics

Techniques	Uses
Functional Magnetic Resonance Imaging	Evaluate the impact of strokes, injuries, and degenerative illnesses like Alzheimer's and Huntington's on cognitive performance.
Susceptibility-weighted Magnetic Resonance Imaging	These conditions include cerebral amyloid angiopathy, traumatic brain damage, vascular abnormalities of the central nervous system, arterial stroke, neurodegenerative disorders, and brain tumours.
FLAIR Magnetic Resonance Imaging	Possible diagnoses include multiple sclerosis, metastatic illness, tuberous sclerosis, and subarachnoid haemorrhage.
Diffusion tensor imaging Magnetic Resonance Imaging	Conditions such as brain tumours, neurodegenerative diseases (such as multiple sclerosis, epilepsy, and Alzheimer's disease), neuropsychiatric disorders (such as schizophrenia), Parkinson's disease, Huntington's disease, Williams syndrome, and fragile X syndrome.
Diffusion-weighted Magnetic Resonance Imaging	Causes of stroke include abrupt cerebral ischemia, brain tumours, white matter illnesses, peripheral nerve imaging, spinal cord damage, and multiple sclerosis.
Brain Volumetric analysis	Possible diagnoses include dementia, multiple sclerosis, epilepsy, and traumatic brain damage.
MR Spectroscopy	Possible causes include brain neoplasms, hereditary metabolic abnormalities, demyelinating illnesses, and infection-related localised lesions.
Double inversion recovery	Identification of demyelinating lesions in individuals with multiple sclerosis, cancer, epileptogenic foci, and cortical abnormalities.
MR Venography	Cerebral venous thrombosis

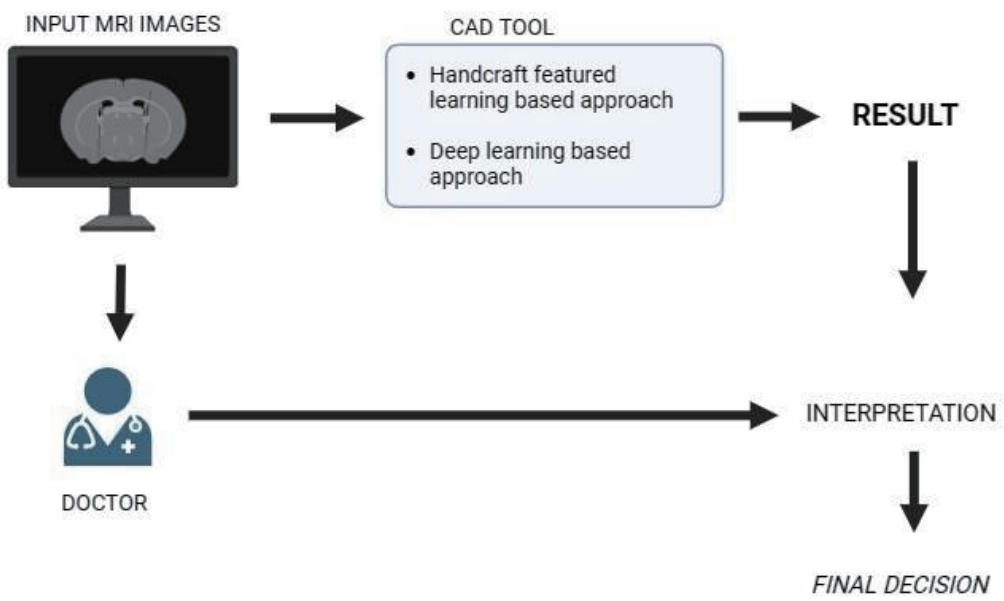

Figure2: Diagrammatic representation of CAD

3.1.1.2 Positron Emission Tomography (PET)

Real-time information on brain activity may be obtained using PET scans. It looks at the binding of neurotransmitter receptors, local blood flow, and brain metabolism. It may identify a wide range of brain disorders, including multiple sclerosis, Parkinson's, Alzheimer's, Huntington's, and several types of dementia. Since it requires the use of a cyclotron to create the beam of photons and radiochemicals for injection into the circulation, the primary barrier to its broad application in clinical diagnostics is its current expensive cost (Politis and Piccini, 2012). Recent studies have concentrated on the early identification and detection of Alzheimer's disease, using positron emission tomography (PET) as a common technique. Before a clinical diagnosis is established, PET may identify illness signs. According to Antoni et al. (2018) and the National Academies of Sciences & Medicine (2023), PET utilizing these tracers may identify Alzheimer's disease in the brain at an unknown stage.

3.1.2 Image Analysis Algorithms

3.1.2.1 Computer-Aided Diagnosis

Neurological disorders encompass a broad range of conditions, including vascular disorders such as stroke, intracerebral hemorrhage, and vascular malformations, degenerative illnesses like Parkinson's and Alzheimer's, and neoplastic diseases like benign brain tumors and potentially fatal cancers. Additionally, inflammatory diseases may arise. The instruments for computeraided diagnosis, or CAD, have come a long way in the last several years. The technology can monitor a patient's health from anywhere at any time thanks to wireless networks. A computer program called CAD reads medical images so that doctors and radiologists may provide second opinions. Radiologists need to give CAD systems the ability to recognize brain abnormalities. CAD system development requires the use of machine learning and pattern recognition algorithms are shown in Fig No. 2 (Gudigar et al., 2020).

In general, brain abnormalities is evaluated utilising two types of CAD systems:

- The approach categorises normal and abnormal brain problems into two or more classes.
- A technique for distinguishing the lesions.

CAD combines many image-processing strategies, including pre-processing, segmentation, feature extraction, dimensionality reduction, and classification.

3.1.2.2 Deep Learning Approaches

Deep learning is the process of training and testing multi-layered neural networks to achieve high degrees of abstraction and comprehend complex structures. Deep learning models fall into two different groups, each of which uses a different approach for sending data across networks. A group of machine learning methods known as "deep learning" (DL) have sparked a great deal of interest in the scientific community because they have surpassed accepted performance benchmarks in voice and image recognition, for example. By obtaining the best representation from raw data via nonlinear transformations, deep learning outperforms traditional machine learning techniques and achieves higher degrees of abstraction and complexity (Rajput DS et al, 2023). Because DL can recognize complex and subtle patterns, it has been employed in neuroimaging studies on mental and neurological diseases. Subtle and extensive changes are hallmarks of these illnesses. Deep learning in neuroimaging has shown promising results, even if it is still in its early phases. This might lead to significant progress in the hunt for imaging-based biomarkers of neurological and psychiatric illnesses. To fully realize the potential of deep learning in neuroimaging, however, more developments are required (Vieira, Pinaya, & Mechelli, 2017).

3.2 Role of Genomics, Proteomics, and Metabolomics in Diagnosis

3.2.1 Genomics

The transcriptome, epigenome, and genome are all examined in genomic investigations of neurological disorders. For genomic research, two technologies are available: array platforms and sequencing. Saliva may also be utilized, however peripheral blood samples are usually used in genomic variation investigations. Transcriptome research primarily focuses on brain tissue because of its importance to the processes underlying illness. The goal of research on CSF and peripheral blood has been to find novel biomarkers. Epigenetic modifications have also been studied using these three tissues. iPSC technologies often make use of skin fibroblasts. Since the nature of neurological ailments may sometimes be ambiguous, it is vital to explore them from a systems approach in order to get a better understanding of them. By comparing the results to those of healthy controls, brain transcriptome studies may uncover dysregulation in disease states by extracting gene expression information at the whole genome level. Microarray systems are the main instrument used in brain transcriptome studies because to their low cost and well-established technology. Since 2008, the sequencing approach has been extensively used,

but because of its high cost, it is often limited to tiny sample quantities.

3.2.1.1 Genetic Markers

Neurodegenerative disease research continues to place a high premium on the development and validation of biomarkers. To find biomarkers that may help with subtyping, predictive prognosis, and preclinical disease diagnosis, a great deal of study has been done. Because these situations are vague, looking for them might be difficult. Monogenic illnesses are caused by deleterious mutations that may result from these genetic markers. Because genetic risk factors interact with the environment and because penetrance varies, the relationship between genetic biomarkers and the development of illness is complex. Significant progress has been achieved in the past several decades in the creation of biomarkers that provide manufacturers and doctors important insights into the vital biochemical processes involved in neurodegenerative diseases. Working in an open science setting will speed up the major scientific cooperation required for biomarker research. Genetic testing may foresee sickness in very specific circumstances and confirm and clarify the diagnosis in people with early-onset neurodegenerative illnesses. The majority of transcriptomics biomarkers and genomes are interdependent. In order to create potent biomarker studies that use deep learning and artificial intelligence and combine a variety of indications, including neuroimaging, there is an increasing need to provide harmonised data across sites. (Singh S, et al, 2023)

3.2.1.2 Next-Generation Sequencing (NGS)

For those who suffer from neurological conditions and their families, learning that they have one may be distressing. The majority of ailments only respond well to treatments meant to impede their progression. The development of next-generation sequencing (NGS) technology in genomic medicine presents new opportunities for the urgent goal of early neurological disease identification and treatment. The time and cost of clinical sequencing have decreased due to advancements in NGS technology, enabling greater investigation and evaluation of genetic variants. Nowadays, whole genome sequencing is less costly than a lot of clinical diagnostic techniques. According to Foo, Liu, and Tan (2013), next-generation sequencing technology may help find novel disease-associated variants and genes for disorders that were previously undetected, as well as assist in the diagnosis of neurological diseases with significant genetic and phenotypic heterogeneity. Subtypes of neurological diseases and applications of NGS are shown in Table No. 2.

3.2.2 Proteomics

Proteomics is important for the diagnosis, prognosis, and follow-up of illnesses. Additionally, it plays a big part in the drug development process as target compounds. Proteomics is the study of protein expression, structure, relationships, activities, and changes across the course of a protein's life cycle. Understanding gene function by proteomics is a valuable technique, despite its greater difficulty compared to genomics. Based on variations in the levels of gene expression, transcriptome or proteome analysis may differentiate between two biological states of a cell. Fig. 3 illustrates the use of proteomics methods.

3.2.2.1 Protein Biomarkers

Protein microarrays, often called protein chips,

Table 2: Subtypes of neurological diseases and applications of NGS

Classes of Neurological Diseases	Examples	Applications of NGS
Neurodevelopmental diseases in childhood	Infantile epilepsy Brain malformation Infantile syndromic seizures	Quick diagnosis with the use of whole genome or exome sequencing Gene discovery Carrier testing Diagnostic screening
Heterogenous monegenic disorders	Parkinsonism Cerebral palsy Mitochondrial diseases	Gene discovery Carrier testing Diagnostic screening
Neuropsychiatric diseases	Autism Schizophrenia Intellectual disability	Performing whole exome or genome-wide sequencing in order to find genes that possess de novo mutations. Risk predictions

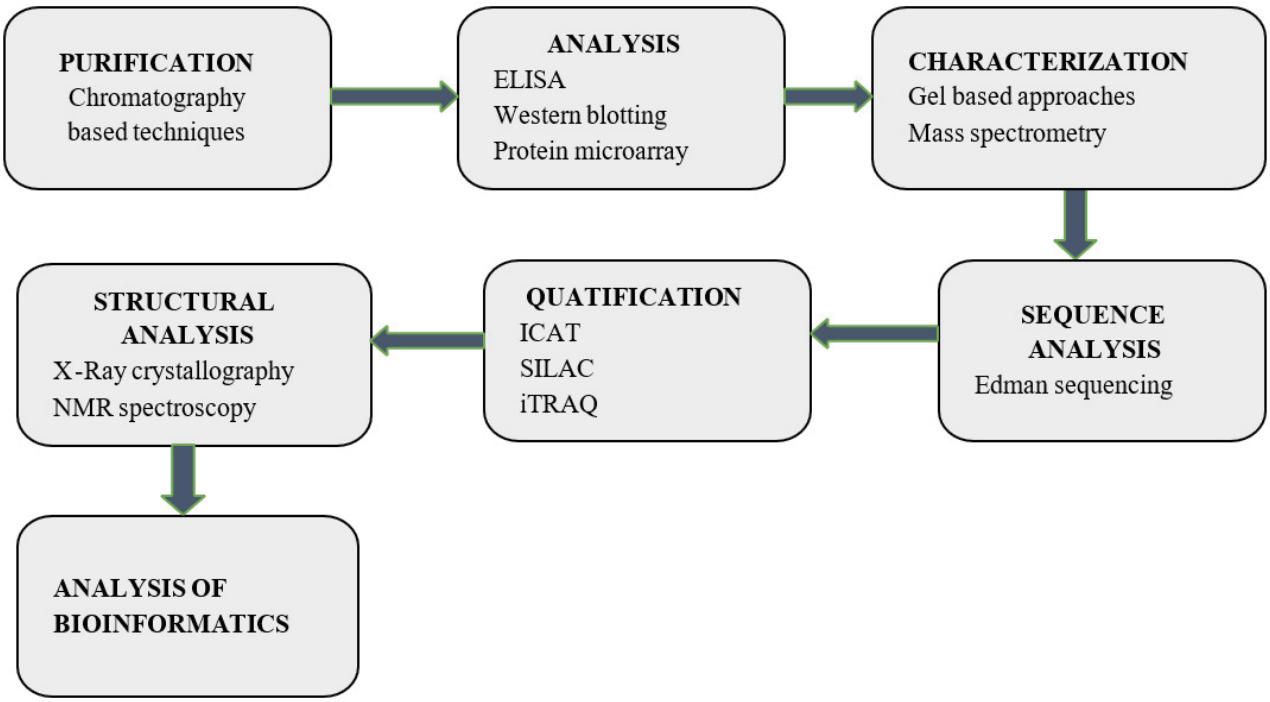

Figure 3: Applications of proteomics techniques

are a new proteomics technology that can identify large amounts of data from tiny samples. Protein microarrays can be categorized as analytical, functional, or reverse-phase.

Functional protein microarray

Purified protein microarrays may be used to investigate interactions between medicines, lipids, proteins, DNA, RNA, and substrates. Investigating the substrate selectivity of yeast protein kinases was the main goal of the functional protein microarray. Numerous proteins' functional characteristics were assessed using the functional protein microarray. Calmodulin-like proteins (CML) and their interactions with CaM substrates were found in a research on protein-protein interactions in A. thaliana.

Reverse-phase protein microarray

These cell lysates are brought about by various biological circumstances, and they are arranged in an orderly manner on nitrocellulose slides before being analyzed using antibodies that are particular to the proteins of interest. Following that, colorimetric, chemiluminescent, and fluorescent techniques were used to identify the antibodies. To make protein measurement easier, reference peptides are put on slides. Proteins that have undergone modifications or are malfunctioning are identified and analyzed using microarrays; these proteins have been connected to certain diseases.

3.2.3 Transcriptomic

Since the fundamental causes of neurological ailments are frequently unknown, it is vital to approach them from a systems perspective in order to get a better understanding of them. By comparing gene expression data from the full genome to healthy controls, brain transcriptome studies may identify dysregulation in disease states. Because cortical thinning is regarded as a morphological marker rather than cortical maturity (Tamnes et al., 2017), cortical structure and function changes with age and are associated with normal cognitive growth (Knickmeyer et al., 2008, Gilmore, Knickmeyer, & Gao, 2018,Giedd & Rapoport, 2010).(Amlien et al., 2016). Many mental illnesses have been connected to changes in the cortical thickness of the brain, namely cortical thinning (Khundrakpam, Lewis, Kostopoulos, Carbonell, & Evans, 2017). It's often believed that abnormal brain maturation trajectories cause cortical thickness discrepancies seen in a number of neurodevelopmental illnesses, including schizophrenia (Gogtay, Vyas, Testa, Wood, Häfner et al., 1994 & Pantelis, 2011). Changes in synapse size and/or neuronal density, as well as the myelination of fibers piercing the cortical mantle, may all contribute to differences in cortical thickness. In order to identify cellular co-relators of these Imaging

Derived Phenotypes, imaging transcriptomic studies have used the expression patterns of specific cell-type marker genes. This has provided insight into the molecular causes of the changes in the brain that occur in both normal and abnormal neurodevelopment (Arnatkeviciute, Fulcher, Bellgrove, & Fornito, 2022).

3.2.3.1 RNA Expression Profiles

Transcripts with more than 200 nucleotides that either don't code for proteins at all or just slightly do so are known as long non-coding RNAs, or lncRNAs. These components play a major role in the transcriptional output of the cell and exhibit functional characteristics like tissue-specific expression, cell fate determination, regulated expression, RNA processing and editing, compensating for variations in gene dosage, genomic imprinting, and conserved evolutionary features. Neurological diseases including Alzheimer's, schizophrenia, Huntington's, and Parkinson's disease have been related to long non-coding variants. Given the prevalence of neurological issues, it is essential to comprehend their underlying causes. Through a variety of mechanisms, including as decoy, scaffolding, miRNA sequestration, histone modification, and transcriptional inhibition, lncRNAs contribute to pathogenesis. The potential of lncRNAs as therapeutic biomarkers may be informed by their involvement (Bhattacharyya, Pandey, Bhattacharyya, & Dey, 2021).

3.2.3.2 Microarray Analysis

The complementary hybridization of nucleic acids is the fundamental idea behind microarray technology (Schena, Shalon, Davis, & Brown, 1995; Lockhart et al., 1996). High-throughput 'dot-blot' technologies, such as gene expression microarrays, link known DNA to a stable platform. The targets are fluorescently marked amplified RNA or complementary DNA (cDNA) species extracted from samples. A DNA microarray is hybridized with a tagged sample, and each probe connects uniquely to its target during this procedure. To assess the intensity of fluorescent signals from probe-bound targets and analyze microarrays, high-resolution fluorescence scanners are used. The quantity of RNA species in the samples is assumed to be proportionate to the signal (Rao, nidagurthi, et al, 2024). 'Transcriptome profiling' of individual samples is made possible by microarrays, which include probes for hundreds of known genes in the human genome. Numerous microarray systems use cDNAs or oligonucleotides. Gene availability, cost, and array size all affect platform selection. Molecular changes linked to disease states may be found in postmortem brains using microarray analysis of gene expression. Certain limitations are specific to postmortem brain research, including small sample sizes and changing clinical characteristics associated with complex diseases. Brain disorders have been associated with dysregulated genes and abnormal patterns of gene expression in recent microarray study (Mirnics & Pevsner, 2004).

3.3 Biomarker Discovery and Validation

A specified property that is assessed as an indication of pathogenic processes, normal biological processes, or biological reactions to exposure or intervention, including therapeutic treatments, is called a biological marker, or biomarker (Cagney et al., 2018). Biomarkers are useful for monitoring disease progression, prognosis, diagnosis, risk assessment, and screening for illnesses. It's critical to identify the target population and the intended use of a biomarker, such as risk screening or stratification, early in the development process.

It's crucial to take into account the patient population, research power (number of samples and events), illness prevalence, validity of biomarker tests, and analytic strategy while doing discovery studies using archival specimens. In order to take into consideration non-biological factors such changes to the chemicals employed in a reaction, people, and machine drift, which might result in batch effects, randomization is required in the creation of biomarkers (Leek et al., 2010). To guarantee a uniform distribution of cases, controls, and specimen age, assign pictures derived from controls and cases at random to arrays, testing plates, or batches (Ransohoff, 2005).

Blinding prevents prejudice resulting from unequal evaluation of biomarker data by keeping the information creators from knowing the scientific outcomes (Ransohoff, 2005). At every step of the research, randomization and blinding should be used to provide reliable biomarker data.

The verb "validation" means "a process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose" . In order to guarantee acceptable expectations, intrinsic updation assesses a molecular marker's performance using resampling techniques like bootstrapping or cross-validation. Extrinsic updation assesses the generation of molecular markers in an individualized dataset that was seldom used at the time of formation. This calls for data from different historical periods, organizations, or geographical areas, as will be covered in the paragraphs that follow. Analytical and clinical biomarker validation are the two forms available

(RaviKKumar VR, et al, 2023).

Analytical validation

Analytical validation entails using a predefined procedure to create a molecular marker production feature, such as reactiveness, particularity, trueness, correctness, and multi-lab repeatability. Rather than focusing on the usability of biomarkers, systematic and scientific corroboration attempts to verify and accomplish biomarkers (continuous measurement of unknown true values) (Gurinderdeep S, et al, 2023) .

Clinical validation

Retrospective utilization of clinical trial data is one method of external validation that involves evaluating biomarkers outside of the original research design. Scientific affirmation aims to establish a link between biosignature and their desired outcome, as well as demonstrate its utility (Ou, Michiels, Shyr, Adjei, & Oberg, 2021).

3.4 Predictive Modelling for Early Detection

One important clinical objective for many neurological disorders is to forecast the disease state. Statistics are made possible by the precise knowledge provided by neuroimaging on the structure and function of the brain. A multinomial logit model with Gaussian process priors is developed to investigate the comparative, thorough clarification of diverse image, methodologies, and brain regions while predicting illness status using whole-brain MRI data. Monte Carlo techniques are used to provide posterior inference on the Advanced Markov Chain model. The suggested model may be used to analyze the importance of different data methods or brain regions in each request since it is descriptive and flexible. Furthermore, it permits accurate assessment of prediction uncertainty, which is necessary for predicting disease stages in clinical contexts (Filippone et al., 2012).

4. Challenges and Opportunities

4.1 Ethical considerations in using computational biology for diagnosis

A large number of the digital biomarker early detection technologies listed above make use of artificial intelligence or machine learning. Implementing them in an ethical and responsible manner presents challenges with regard to the application area, data source, and analytic method. The World Health Organization and the European Commission are two well-known institutions that have released recommendations for thinking about "AI ethics" in the context of treatment. According to Ford, Milne, and Curlewis (2023), the methods frequently rely on commonly held beliefs that encompass core principles of medical ethics, such as kindness, nonmaleficence, fairness, and respect for autonomy, with an emphasis on clearance, explainable, definability, openness, management, and liabilities.

Precision health uses data from a variety of sources, including routine, environmental, social media, medical records, and health insurance claims, to offer personalized health care, prevent and identify disease, and provide appropriate treatments and cures. This results in significant advantages for sensing technologies (like EHRs), computations (like machine learning), and transmission (like communications across health data centers). Careful attention is always required since health records include sensitive private information, including the identity of the patient and caregiver as well as the patient's medical problems. The disclosure of such confidential data may have detrimental effects on an individual's life, including psychological distress, increased security costs, and loss of employment due to health issues (Thapa & Camtepe, 2021).

4.2 Future directions and potential advancements in the field

4.2.1 CRISPR/Cas9 and gene-editing in neurodegenerative disorders

Millions of people worldwide suffer from a range of degenerative diseases that are linked to genetic abnormalities. While many genetic anomalies may not show any symptoms until adulthood, others can be identified in the early stages of infancy. As a result, Huntington's disease (HD), an uncommon intrinsic neurodegenerative illness that causes nerve cells in the mind to break down and die, is characterized by atypical involuntary movement disorders that typically manifest until adulthood. For the majority of inherited illnesses, treatment options are few, if they exist at all. Techniques for editing genes include CRISPR, effector nucleases that mimic transcription activators (TALENs), mega nucleases, nucleases with zinc fingers (ZFNs), and CRISPR (Gurinderdeep S. et al, 2024)

Cas9 are used for modifying genes, have generated significant interest as potential treatments for specific neurodegenerative diseases. These tools have the ability to edit, replace, and modify faulty regions of the genome.

Specific foreign nucleic acid sequences may be targeted by the bacterial adaptive immune system known as CRISPR (Jansen, Embden, Gaastra, & Schouls, 2002). Miniature, recurring, self-complementary

sequences and other chronologies encoding Cas proteins divide unique spacer sequences that make up CRISPR (Makarova, Koonin,Grishin, & Wolf, 2006). Gene editing in eukaryotes has shown promise using the CRISPR-Cas9 system, which was first derived from S. pyogenes (Barrangou et al., 2007). The CRISPR-Cas 9 system has been thoroughly explored, and as a result, it can now be used for gene editing tasks including introducing desired genetic modifications and correcting mutated regions of the genome. Joung and Sanders, 2014).

In order to designate the DNA for clear-cut DSBs, other gene editing techniques like TALENs and ZFNs need special planning, which adds to the already time-consuming and expensive process (Mao et al., 2013). Cleavage, size, off-target, and cytotoxicity are other problems (Carlson, Fahrenkrug, & Hackett, 2012). ZFNs exhibit cytotoxicity and off-target effects, and their effectiveness is restricted (Kim & Kim, 2014). While TALENs are more effective than ZNFs, they are still required for a number of neurological conditions that are inherited and for which there are now no effective treatments. Due to misunderstandings of the intricate processes of the brain, including the hereditary components of many neurodegenerative diseases and their unclear origin, the treatment of neurological disorders is now restricted. These traits obstruct the development of novel pharmaceutical targets. Pathogenic microbe identification (Kolli, Lu, Maiti, Rossignol, & Dunbar, 2018).

4.2.2 Advancements in computational models and algorithms

Advances in scientific and computerized neuroscience, along with high-performance computers, have led to a rapid surge in the creation of computational models to research neural disease causes.(refer to Figure 3). In the foreseeable future, researchers and scientists will focus on developing computational models to deliver effective therapeutic and pharmaceutical solutions (Gandolfi, Boiani, Bigiani, & Mapelli, 2021). Computational models and algorithms are shown in Fig:4.

5. Conclusion

As technology and our knowledge of disease processes have advanced, so too has the role of computational biology in the diagnosis of neurodegenerative disorders. It integrates many data types genomic, transcriptomic, proteomic, and clinical—to gain understanding of the intricate mechanisms underlying neurodegenerative diseases.

Computational biologists and clinicians working

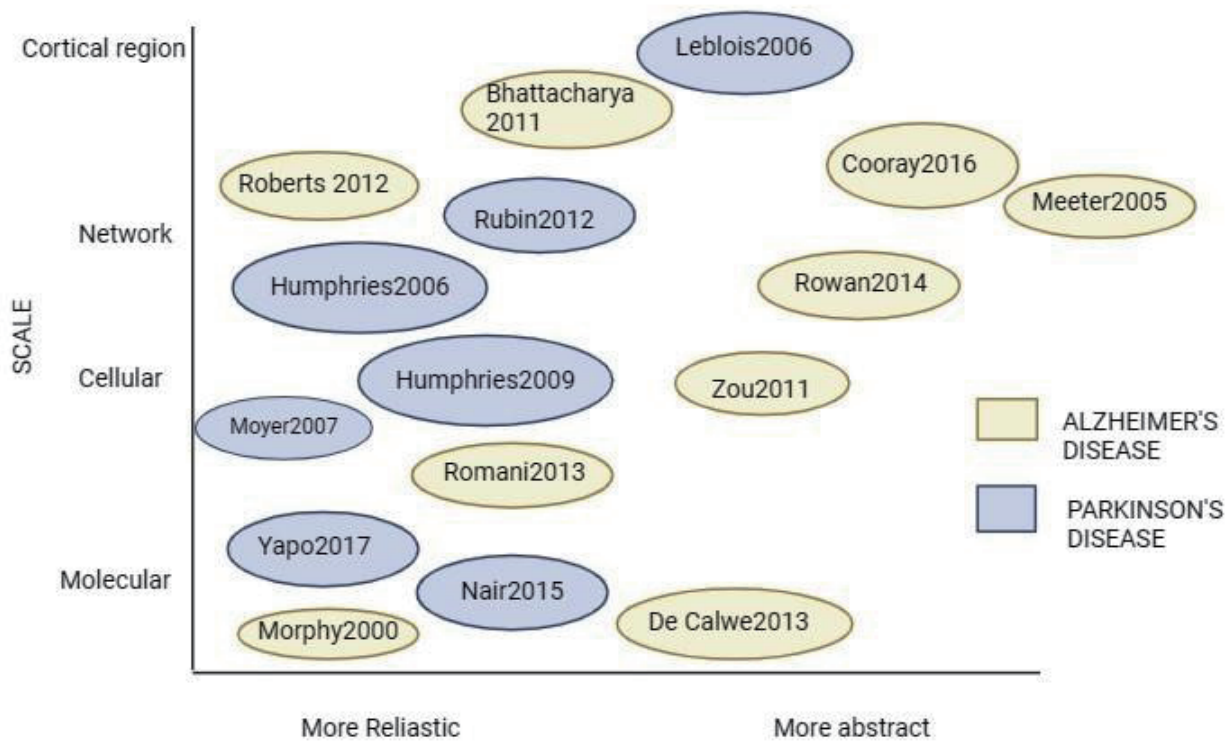

Figure 4: Computational models

together is essential to advancing our knowledge of neurodegenerative diseases and applying research results to therapeutic settings. All things considered, computational biology holds great promise for improving our knowledge of neurodegenerative diseases and creating diagnostic and treatment approaches for these crippling disorders. In conclusion, early detection, precision medicine, the integration of multi-omics data, cutting-edge technologies, and cooperative research efforts will all shape the future of neurodegenerative disorder diagnosis and improve outcomes for patients with these crippling illnesses.

Conflict of interest

There are no conflicting interests, as the authors have stated.

References

1 Abeliovich, A., & Gitler, A. D. (2016). Defects in trafficking bridge Parkinson's disease pathology and genetics. Nature, 539(7628), 207-216.

2 Aizawa, H., Amo, R., & Okamoto, H. (2011). Phylogeny and ontogeny of the habenular structure. Frontiers in neuroscience, 5, 138.

3 Alzheimer's disease and some therapeutic approaches targeting Aβ by using several synthetic and herbal compounds. Oxidative medicine and cellular longevity, 2016.

4 Amlien, I. K., Fjell, A. M., Tamnes, C. K., Grydeland, H., Krogsrud, S. K., Chaplin, T. A., Walhovd, K. B. (2016). Organizing principles of human cortical development—thickness and area from 4 to 30 years: insights from comparative primate neuroanatomy. Cerebral cortex, 26(1), 257-267.

5 Armstrong, M. J., & Okun, M. S. (2020). Diagnosis and treatment of Parkinson disease: a review. Jama, 323(6), 548-560.

6 Arnatkeviciute, A., Fulcher, B. D., Bellgrove, M. A., & Fornito, A. (2022). Imaging transcriptomics of brain disorders. Biological Psychiatry Global Open Science, 2(4), 319331.

7 Bađun, M. (2019). Alzheimer Europe. In Encyclopedia of Gerontology and Population Aging (pp. 1-5): Springer International Publishing.

8 Barrangou, R., Fremaux, C., Deveau, H., Richards, M., Boyaval, P., Moineau, S.,Horvath, P. (2007). CRISPR provides acquired resistance against viruses in prokaryotes.Science, 315(5819), 1709-1712.

9 Bhattacharyya, N., Pandey, V., Bhattacharyya, M., & Dey, A. (2021). Regulatory role of long non coding RNAs (lncRNAs) in neurological disorders: From novel biomarkers to promising therapeutic strategies. Asian journal of pharmaceutical sciences, 16(5), 533-550.

10 Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. The Lancet, 397(10291), 2284-2303.

11 Borrell, V., & Calegari, F. (2014). Mechanisms of brain evolution: regulation of neural progenitor cell diversity and cell cycle length. Neuroscience research, 86, 14-24.

12 Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules, 25(24), 5789.

13 Cagney, D. N., Sul, J., Huang, R. Y., Ligon, K. L., Wen, P. Y., & Alexander, B. M. (2018). The FDA NIH Biomarkers, EndpointS, and other Tools (BEST) resource in neuro-oncology. Neuro-oncology, 20(9), 1162-1172.

14 Carlson, D. F., Fahrenkrug, S. C., & Hackett, P. B. (2012). Targeting DNA with fingers and TALENs. Molecular therapy-Nucleic acids, 1.

15 Chicco, D. (2017). Ten quick tips for machine learning in computational biology. BioData mining, 10(1), 35.

16 Cortical thickness abnormalities in autism spectrum disorders through late childhood, adolescence, and adulthood: a large-scale MRI study. Cerebral Cortex, 27(3), 1721-1731.

17 De-Paula, V. J., Radanovic, M., & Diniz, B. S. (2012). and Orestes V. Forlenza. Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease, 65, 329.

18 Dulovic, M. (2018). Genotype-phenotype relations for the Parkinson's disease genes Parkin, PINK1, DJ1: MDSGene systematic review. Movement Disorders, 33(5), 730-741.

19 Feigin, V. L., Nichols, E., Alam, T., Bannick, M. S., Beghi, E., Blake, N., . . . Ellenbogen, R. G. (2019). Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology, 18(5), 459-480.

20 Feigin, V., Nichols, E., Alam, T., Bannick, M., Beghi, E., Blake, N., . . . Ellenbogen, R. (2019). GBD 2016 Neurology Collaborators: Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol, 18(5), 459-480.

21 Filippone, M., Marquand, A. F., Blain, C. R., Williams, S. C., Mourão-Miranda, J., & Girolami, M. (2012). Probabilistic prediction of neurological disorders with a statistical assessment of neuroimaging data modalities. The annals of applied statistics, 6(4), 1883.

22 Foo, J. N., Liu, J., & Tan, E.-K. (2013). Next-generation sequencing diagnostics for neurological diseases/disorders: from a clinical perspective. Human genetics, 132, 721-734.

23 Ford, E., Milne, R., & Curlewis, K. (2023). Ethical issues when using digital biomarkers and artificial intelligence for the early detection of dementia. Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery, e1492.

24 Gaenslen, A., Swid, I., Liepelt-Scarfone, I., Godau, J., & Berg, D. (2011). The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. Movement Disorders, 26(4), 653-658.

25 Gandolfi, D., Boiani, G. M., Bigiani, A., & Mapelli, J. (2021). Modeling neurotransmission: Computational tools to investigate neurological disorders. International Journal of Molecular Sciences, 22(9),

4565.
26 Georges, J., Miller, O., & Bintener, C. (2020). Estimating the prevalence of dementia in Europe. Report N.
27 Giedd, J. N., & Rapoport, J. L. (2010). Structural MRI of pediatric brain development: what have we learned and where are we going? Neuron, 67(5), 728-734.
28 Gilmore, J. H., Knickmeyer, R. C., & Gao, W. (2018). Imaging structural and functional brain development in early childhood. Nature Reviews Neuroscience, 19(3), 123-137.
29 Gitler, A. D., Dhillon, P., & Shorter, J. (2017). Neurodegenerative disease: models, mechanisms, and a new hope. Disease models & mechanisms, 10(5), 499-502.
30 Gogtay, N., Vyas, N. S., Testa, R., Wood, S. J., & Pantelis, C. (2011). Age of onset of schizophrenia: perspectives from structural neuroimaging studies. Schizophrenia bulletin, 37(3), 504-513.
31 Gudigar, A., Raghavendra, U., Hegde, A., Kalyani, M., Ciaccio, E. J., & Acharya, U. R. (2020). Brain pathology identification using computer aided diagnostic tool: A systematic review. Computer Methods and Programs in Biomedicine, 187, 105205.
32 Gurinderdeep Singh, Tanmay Khullar, Green Solvents and Sustainable Catalysis: Applications in Organic Synthesis, JCHR (2023) 13(5), 829-838| ISSN:2251-6727.
33 Gurinderdeep Singh, Tanmay Khullar, In Silico ADMET Analysis of Turmeric Compounds for Drug Likeness, JCHR (2024) 14(1), 926-936| ISSN:2251-6727.
34 Häfner, H., Maurer, K., Löffler, W., Fätkenheuer, B., Der Heiden, W. A., Riecher-Rössler, A., . . . Gattaz, W. (1994). The epidemiology of early schizophrenia: influence of age and gender on onset and early course. The British journal of psychiatry, 164(S23), 29-38.
35 Jansen, R., Embden, J. D. v., Gaastra, W., & Schouls, L. M. (2002). Identification of genes that are associated with DNA repeats in prokaryotes. Molecular microbiology, 43(6), 15651575.
36 Kasten, M., Hartmann, C., Hampf, J., Schaake, S., Westenberger, A., Vollstedt, E. J., . . .
37 Khundrakpam, B. S., Lewis, J. D., Kostopoulos, P., Carbonell, F., & Evans, A. C. (2017).
38 Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., . . . Zoing, M. C. (2011). Amyotrophic lateral sclerosis. The Lancet, 377(9769), 942-955.
39 Kim, H., & Kim, J.-S. (2014). A guide to genome engineering with programmable nucleases.
40 Knickmeyer, R. C., Gouttard, S., Kang, C., Evans, D., Wilber, K., Smith, J. K., . . . Gilmore, J. H. (2008). A structural MRI study of human brain development from birth to 2 years. Journal of neuroscience, 28(47), 12176-12182.
41 Kolli, N., Lu, M., Maiti, P., Rossignol, J., & Dunbar, G. L. (2018). Application of the gene editing tool, CRISPR-Cas9, for treating neurodegenerative diseases. Neurochemistry international, 112, 187-196.
42 Koonin, E. V., Makarova, K., Grishin, N., & Wolf, Y. I. (2006). A putative RNAinterference-based immune system in prokaryotes: the epitome of prokaryotic genomic diversity. Paper presented at the SYMPOSIA-SOCIETY FOR GENERAL MICROBIOLOGY.
43 Leek, J. T., Scharpf, R. B., Bravo, H. C., Simcha, D., Langmead, B., Johnson, W. E., . . . Irizarry, R. A. (2010). Tackling the widespread and critical impact of batch effects in highthroughput data. Nature Reviews Genetics, 11(10), 733-739.
44 Li, J., & Wang, G.-Z. (2019). Application of computational biology to decode brain Transcriptomes. Genomics, Proteomics & Bioinformatics, 17(4), 367-380.
45 Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., . . . Cooper, C. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet, 396(10248), 413-446.
46 Lockhart, D. J., Dong, H., Byrne, M. C., Follettie, M. T., Gallo, M. V., Chee, M. S., . . . Norton, H. (1996). Expression monitoring by hybridization to high-density oligonucleotide arrays. Nature biotechnology, 14(13), 1675-1680.
47 Mao, Y., Zhang, H., Xu, N., Zhang, B., Gou, F., & Zhu, J.-K. (2013). Application of the CRISPR–Cas system for efficient genome engineering in plants. Molecular plant, 6(6), 2008-2011.
48 Mirnics, K., & Pevsner, J. (2004). Progress in the use of microarray technology to study the neurobiology of disease. Nature neuroscience, 7(5), 434-439.
49 Nature Reviews Genetics, 15(5), 321-334.
50 Ou, F.-S., Michiels, S., Shyr, Y., Adjei, A. A., & Oberg, A. L. (2021). Biomarker discovery and validation: statistical considerations. Journal of Thoracic Oncology, 16(4), 537-545.
51 Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. (2014). The prevalence of Parkinson's disease: a systematic review and meta-analysis. Movement Disorders, 29(13), 1583-1590.
52 R. (2018). Genotype-phenotype relations for the Parkinson's disease genes SNCA, LRRK2, VPS35: MDSGene systematic review. Movement Disorders, 33(12), 1857-1870.
53 Rajput DS, Gupta N, Singh S, Sharma B. A Comprehensive Review: Personalized Medicine for Rare Disease Cancer Treatment. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2023 Dec 23;39:e20230008. doi: 10.62958/j.cjap.2023.008. PMID: 38830754.
54 Ransohoff, D. F. (2005). Bias as a threat to the validity of cancer molecular-marker research. Nature Reviews Cancer, 5(2), 142-149.
55 Rao, nidagurthi & chitrapu, prashanti & singh, gurinderdeep & pulipati, sowjanya & veluru, hari. (2024). Synthesis and in silico Assessment of Heteroaryl Semicarbazones: Towards Understanding Antimicrobial Activities and Safety Profiles. Asian Journal of Chemistry. 36. 1135-1141. 10.14233/ajchem.2024.31388.
56 RaviKKumar VR, Rathi S, Singh S, Patel B, Singh S, Chaturvedi K, Sharma B. A Comprehensive Review on Ulcer and Their Treatment. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2023 Dec 21;39:e20230006. doi:

10.62958/j.cjap.2023.006. PMID: 38755116.

57 Sander, J. D., & Joung, J. K. (2014). CRISPR-Cas systems for editing, regulating and targeting genomes. Nature biotechnology, 32(4), 347-355.

58 Schena, M., Shalon, D., Davis, R. W., & Brown, P. O. (1995). Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science, 270(5235), 467470.

59 Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. Cold Spring Harbor perspectives in medicine, 1(1), a006189.

60 Singh S, Chaurasia A, Gupta N, Rajput DS. Effect of Formulation Parameters on Enalapril Maleate Mucoadhesive Buccal Tablet Using Quality by Design (QbD) Approach. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2024 Jun 27;40:e20240003. doi: 10.62958/j.cjap.2024.003. PMID: 38925868.

61 Singh S, Chaurasia A, Rajput DS, Gupta N. Mucoadhesive Drug Delivery System and There Future Prospective: Are a Promising Approach for Effective Treatment? Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2023 Dec 20;39:e20230005. doi: 10.62958/j.cjap.2023.005. PMID: 38751344.

62 Singh, Gurinderdeep & Mohandoss, Kiruba & Shah, Tora & Dixit, Ritesh & Arul, Vettrivel & Verma, Dr & Rathi, Sanjesh & Parvez, Nayyar. (2024). Potential role of 3D Printing in Cosmeceuticals: Systematic Review. Volume 6. 824 -855. 10.33472/AFJBS.6.10.2024.823-853.

63 Singh, S. K., Srivastav, S., Yadav, A. K., Srikrishna, S., & Perry, G. (2016). Overview of

64 Spires-Jones, T. L., & Hyman, B. T. (2014). The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron, 82(4), 756-771.

65 Tamnes, C. K., Herting, M. M., Goddings, A.-L., Meuwese, R., Blakemore, S.-J., Dahl, R. E., . . . Crone, E. A. (2017). Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness. Journal of neuroscience, 37(12), 3402-3412.

66 Taylor, J. P., Brown Jr, R. H., & Cleveland, D. W. (2016). Decoding ALS: from genes to mechanism. Nature, 539(7628), 197-206.

67 Thapa, C., & Camtepe, S. (2021). Precision health data: Requirements, challenges and existing techniques for data security and privacy. Computers in biology and medicine, 129, 104130.

68 Trinh, J., Zeldenrust, F. M., Huang, J., Kasten, M., Schaake, S., Petkovic, S., . . . König, I.

69 Vieira, S., Pinaya, W. H., & Mechelli, A. (2017). Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications. Neuroscience & Biobehavioral Reviews, 74, 58-75.

70 Wilson, D. M., Cookson, M. R., Van Den Bosch, L., Zetterberg, H., Holtzman, D. M., & Dewachter, I. (2023). Hallmarks of neurodegenerative diseases. Cell, 186(4), 693-714.

71 Wyss-Coray, T. (2016). Ageing, neurodegeneration and brain rejuvenation. Nature, 539(7628), 180-186.

72 Yang, Y., Wang, H., Hu, J., & Hu, H. (2018). Lateral habenula in the pathophysiology of depression. Current opinion in neurobiology, 48, 90-96.

73 Yiannopoulou, K. G., & Papageorgiou, S. G. (2020). Current and future treatments in Alzheimer disease: an update. Journal of central nervous system disease, 12, 11795735209073.