A SYSTEMATIC REVIEW ON EARLY DIAGNOSIS AND INTERVENTION STRATEGIES OF ALZHEMERS DISEASE FROM BIOMARKERS TO THERAPEUTIC APPROACHES

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Abstract: Alzheimer's disease (AD) is predicted to become much more common as the world's population ages, posing a serious threat to global health. Effective intervention and treatment depend on early discovery, yet the diagnostic techniques used today are often invasive, expensive, and time-consuming. This study examines a range of procedures and biomarkers for the early identification of AD, from cutting-edge non-invasive and minimally invasive techniques like EEG, ocular imaging technologies, and blood/saliva/urine biomarkers, to traditional methods like brain imaging and CSF analysis. We talk about how crucial it is to find biomarkers for AD that can identify the disease in its preclinical or early clinical phases so that appropriate action may be taken before irreversible cognitive loss happens. Potential methods for early diagnosis are discussed, including speech testing, subjective memory complaints assessment, late-onset depression evaluation, and episodic memory tests. In addition, we look at standard biomarkers such as CSF tau levels and amyloid β, as well as brain imaging techniques like PET and SPECT scans. The emerging non-invasive and minimally invasive biomarkers that show promise in predicting the presence of AD are discussed in this review, along with ocular imaging methods like OCT and OCTA and blood, saliva, and urine biomarkers that measure electrical activity. Although these biomarkers may be more accessible and user-friendly, standardization and validation across a range of populations are still crucial. We talk about the latest developments in AI and machine learning methods for merging and evaluating multi-modal data, which provide insights into customized forecasting and long-term tracking of AD development. In conclusion, we provide an overview of the major research projects and approaches included in the review, emphasizing their contributions to the area of early Alzheimer's disease detection.

Keywords: Alzheimer's disease (AD); biomarkers; low, Machine learning algorithms, Imaging technologies

1. INTRODUCTION

A typical neurodegenerative brain illness that affects a sizable section of the populace is Alzheimer's disease (Promotion). Up to 75% of all instances of dementia, a main cause of mortality, are caused by it. Cognitive decline and cognitive capability slowly decay as a result of Promotion [1] [2].

Alzheimer's disease (Promotion) affects in excess of 35 million individuals around the world and is the main cause of dementia in the old. The maturing populace in rich nations suggests that until treatments for anticipation or fix are discovered, Promotion will spread far and wide. Lamentably, among individuals with symptomatic Promotion, most of trial therapies expected to change the illness make not shown any clinical impacts. The medications were most likely administered past the point of no return in the Promotion neuropathological processes, which is the reason this disappointment happened. Finding biomarkers that are responsive to Promotion in its preclinical or early clinical phases is urgent for empowering prior intervention and perhaps more successful treatment approaches. Current treatment studies are assessing the obscure expected advantages of starting treatment at the preclinical stage of Promotion [3]. [4].

In maturing communities, dementia is one of the principal medical problems [17] [18]. As per estimates from the World Wellbeing Association, there are around 10 million new instances of dementia internationally every year, with 60-70% of those cases being Alzheimer's disease (Promotion) individuals [19]. The weight of Promotion in the following decade will be enormous, influencing hundreds of millions of individuals, their families, and the country's medical services systems, mostly in industrialized nations because of maturing patterns [20]. As per epidemiological studies, one out of three Americans beyond 85 years old will have Promotion [21], and the extent of Americans north of 85 will fourfold by 2050 [22]. One of the best five causes of death in created nations is Promotion. Besides, it is the main illness anticipated to increase by a sufficiently significant room for error to surpass any remaining diseases in the following decades [23]. Thus, these tendencies really must be reversed around the world.

1.1. Diagnosis

As of the present moment, a specialist facility is required for the clinical diagnosis of Alzheimer's disease (Promotion), which calls for various tests such as a clinical assessment, neuropsychological testing, neuroimaging, cerebrospinal fluid (CSF) analysis, and blood work. Be that as it may, this is not a period or cash proficient strategy, and as the total populace

ages, more instances of Promotion are anticipated, and there won't be sufficient specialist clinics to deal with the increasing interest. In spite of the fact that CSF and neuroimaging indicators are viewed as the highest quality levels for assessing patients in vivo, they are pricy, intrusive, and unsuitable for use as essential diagnostic or screening instruments. Finding clinically applicable screening and diagnostic methods is critical since nonspecialist physicians have been shown to be mistaken in diagnosing early Promotion and gentle cognitive impairment (MCI) [3][5]. Consequently, there is an increasing requirement for minimal expense, painless methods to identify individuals with Alzheimer's disease (Promotion) who are in the preclinical or early clinical phases of the illness. With the use of these instruments, forefront location might be made possible, trailed by clinical, CSF, and neuroimaging investigations in specialty clinics. Medical services systems would benefit significantly from having the option to expect a singular's risk of gaining Promotion since it would empower early, intensive lifestyle consultations and drug therapies for high-risk patients. The need of early Promotion diagnosis has been built up by ongoing discoveries in neuropathology, biochemistry, and neuroimaging that demonstrate the presence of Promotion biomarkers in the brains and CSF of elderly folks individuals who are cognitively sound [3] [6].

Two essential drivers lead to brain alterations in individuals with Alzheimer's disease (Promotion):

(1) the development of beta-amyloid protein fragments outside of neurons, which causes plaques to create.

(2) the development of tau protein inside neurons, which ultimately causes tangles to create. While tau tangles disable the development of essential chemicals inside neurons, resulting in the loss of neuronal transmission, beta-amyloid plaques develop over the long haul at synapses between neurons. Consequently, the brain experiences extremely durable alterations, such as decay or shrinking in the hippocampus, transient parietal, and cerebrums as a consequence of cell demise, which is remembered to happen when microglia can't complete their typical tasks. The Worldwide Disintegration Scale (GDS), which aids in foreseeing the key degenerative process of dementia and its phases, divides the severity of dementia, especially Promotion, into seven stages. [1] [7].

1.2. The importance of an early diagnosis

In the past, Promotion has just been diagnosed in the last option stages of the illness, which has prompted exclusion. Nevertheless, the disease process might require years to finish, putting a significant weight on the patient, parental figure, and medical services system along the way[8]. Point of fact, decreasing the heap on the medical services system and further developing patient outcomes rely upon the early ID and diagnosis of Promotion. Essential consideration physicians, or PCPs, are essential in spotting early signs of Promotion and sending patients for additional testing and diagnosis. PCPs should know about the best reference routes to specialists for additional diagnostic testing and approach trustworthy and demonstrated screening instruments for assessing cognitive impairment in their patients. Moreover, PCPs can assist patients and their families with understanding the early admonition signs and symptoms of Promotion as well as the worth of early diagnosis and treatment. This could incorporate making lifestyle changes, such exercising and eating a fair eating routine, which can assist with bringing down the possibility growing Promotion or postpone its start. Also, PCPs might team up with patients and their families to make care plans that consider the mind boggling clinical and social requirements of Promotion patients. [8] [9].

Precise ID of Alzheimer's disease is essential for future preparation and the board. A specialist's assessment is not by any means the only diagnostic strategy that might be used to assist with diagnosing Alzheimer's. MRIs, PET scans, and neuropsychological testing are a couple of examples of these, as are blood tests to preclude other possible reasons of cognitive loss. It is significant that the opportune distinguishing proof and diagnosis of Alzheimer's disease might improve treatment results and hoist the standard of living for both the impacted person and their relatives [10] [11].

2. STRATEGY FOR EARLY DETECTION OF ALZHEIMER'S DISEASE

Instead, then, at that point, contingent just upon one diagnostic strategy, Alzheimer's disease is usually diagnosed using a blend of diagnostic techniques. Clinical practitioners use a scope of instruments and strategies, frequently consulting with experts such neuropsychologists, neurologists, geriatricians, and geriatric psychiatrists. Brain scans using magnetic resonance imaging (MRI), figured tomography (CT), or positron emission tomography (PET) are frequently performed to affirm an Alzheimer's diagnosis or preclude other possible causes of symptoms. In any case, sometimes, especially in the early stages, diagnostic evaluations may not recognize Alzheimer's disease, necessitating further testing. Besides, moderate cognitive impairment (MCI) may go before Alzheimer's disease advancement by numerous years in individuals who start with MCI and afterward progressively push toward Alzheimer's. Few out of every odd person with gentle cognitive im-

pairment (MCI) will progress to Alzheimer's disease, and different methods, including blood plasma spectroscopy and clinical imaging, might be used to forecast the likelihood of conversion. [1] [12].

2.1. Episodic memory tests

The cognitive space most severely affected by Alzheimer's disease (Promotion) and its prodromal phases, such as amnestic gentle cognitive impairment (aMCI), is episodic memory. Tests like the California Verbal Learning Test (CVLT-II), the Free and Prompted Selective Reminding Test (FCSRT), and the Consistent Memory subtest from the Wechsler Memory Scale may be in every way used to assess episodic memory. Contrasting these tests has driven studies with presume that CVLT is more sensitive to preclinical alterations in episodic memory. With regards to foreseeing which individuals with memory problems could have episode Promotion throughout the span of two to four years, the FCSRT's free review has shown to be more precise than the Wechsler Coherent Memory instant review. Moreover, among standardized neuropsychological batteries, the FCSRT has shown to be the most specific and sensitive test for prodromal Promotion diagnosis in previous investigations. Furthermore, the FCSRT beat the Wechsler Consistent Memory postponed review in foreseeing the opportunity that a Promotion like cerebrospinal fluid (CSF) profile will happen in MCI participants [3] [13].

2.2. Clinical tests Assessment of subjective memory complaints

It's basic to separate, while discussing cognitive downfall, between subjective memory complaints (SMC) expressed by persons or informants (relatives, caretakers, or doctors) and objective deficiencies assessed with specific neuropsychological tests. The job of SMCs in preclinical Promotion diagnosis is a subject of developing interest and discussion. As per ongoing research, SMCs are connected to unusual brain amyloid gathering in more seasoned individuals who are cognitively ordinary as well as an increased risk of late-onset Promotion, which develops before any discernible cognitive loss. Pre-MCI SMCs have also been found in a research including bearers of the PSEN1 E280 A transformation. As per a new research, cognitive impairment detailed by informants was associated with a more noteworthy recurrence of MCI. Among persons north of 50 visiting essential consideration facilities with SMC, 33% as of now had MCI. Thus, information from the two persons and informants is essential for screening, and SMC might work as a signal of preclinical and early symptomatic Promotion. Aside from personality traits and depression, noninvasive and reasonable diagnostic tools for assessing SMC, similar to the Subjective Cognitive Failures Questionnaire or straightforward inquiries about memory impairment and concerns, might be suitable as additional parameters for a more comprehensive screening of putatively amyloidpositive however otherwise cognitively sound individuals [3] [14].

2.3. Assessment of late-onset depression

One of every five individuals will at some time in their lives suffer depression, making it a widespread event. Similarly, dementia is a typical illness in later life; the possibility getting it doubles like clockwork after 65 and may arrive at half in those more than 90. In spite of the fact that research has shown that depression and late-onset dementia frequently coexist, it is not clear the way in which the two are connected. Studies show that neuropathology associated with Alzheimer's disease might be associated with depression in ladies conveying the presenilin-1 transformation in the preclinical stage of familial Promotion [15]. Depression or depressed symptoms might be a sign of one of three things: (1) a dementia risk factor, (2) a prodromal stage of dementia, or (3) a result of the neurodegenerative processes that cause dementia. A drawn out research by Barnes and colleagues found that a person's own history of depression might raise their possibility procuring dementia at a later age. Contingent upon when in life depression strikes, the type of dementia might change. Specifically, the study discovered that individuals with depressive symptoms in their later years had a twofold higher possibility getting Alzheimer's disease (Promotion), whereas individuals with symptoms in their mid-and late-life had a triple higher possibility getting vascular dementia (VaD) [3] [15].

2.4. Speech testing

The mind boggling process of verbal correspondence calls on different cognitive skills, including word meaning and syntactic comprehension, phonological structural information, and memory. Language is a significant organic sample to look at since it is spontaneously made by individuals consistently and is promptly recordable. Decay of speech affects a person's ability for social connection and frequently leads to close to home changes, the two of which are early indicators of Alzheimer's disease. Anybody in the patient's ordinary surroundings might use programmed speech analysis methods to recognize these changes since they don't require specialist expertise [3] [16].

3. CONVENTIONAL BIOMARKERS

The recognizable proof of biomarkers is significant in the early ID of Promotion disease risk preceding the onset of dementia (Figure 1). These biomarkers might be used as reference approval procedures for other elective biomarkers tracked down in human organic fluids and are currently pertinent in therapeutic settings. The Public Institute on Maturing and Alzheimer's Association's 2018 research structure, which modifies previous procedures for Promotion diagnostic recommendations to focus on biomarkers as opposed to starting symptom assessment, provides the establishment for the recently used biomarkers for Advertisement diagnosis [24].

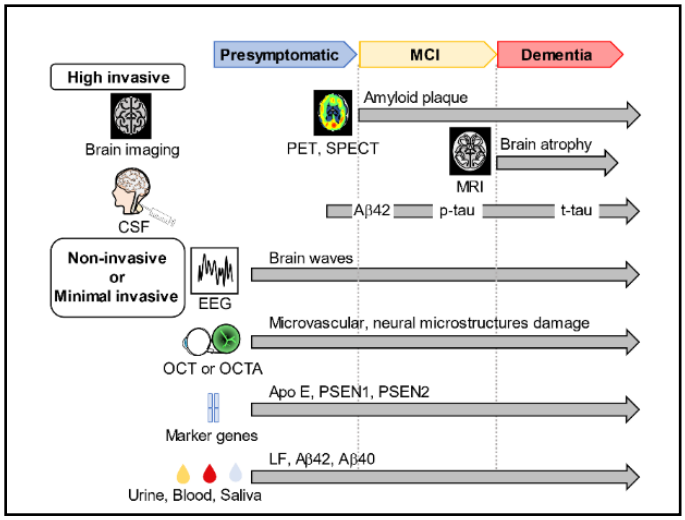

Figure 1: Promotion biomarker screening techniques. Customary biomarkers for Alzheimer's disease (Promotion) incorporate atomic magnetic resonance (NMR) to assess structural alterations in the brain and positron emission tomography (PET) and single-photon emission registered tomography (SPECT) to assess brain capability. Amyloid β 42 (Aβ42), phosphorylated tau (p-tau), and absolute tau (t-tau) levels in cerebrospinal fluid are examples of Promotion biomarkers. New biomarkers have been discovered, including Promotion marker genes, electroencephalograms (EEG) for checking brain waves, and optical rationality tomography (OCT) and optical lucidness tomography angiography (OCTA) for assessing abnormalities in the blood vessels of the eyes. Furthermore, Promotion causing genes and biomarkers in saliva, blood, and pee have been discovered. Furthermore, biomarkers in saliva, blood, and pee have been found.

Since the early 1990s, the Braak-staging order of Promotion has been a usually used diagnostic strategy for assessing the various stages of Promotion in various parts of the brain. In ongoing research published in 2021, tau-based and Aβ-based PET scan biomarkers were assessed using the Braak stages. That's what research shown, in comparison to using just an Aβ PET scan, the blend of a tau-PET scan and Braak staging is promising for anticipating patient-specific risks of clinical Promotion improvement [25] [26].

3.1. Brain Imaging

Using dynamic scientific models, single-photon emission processed tomography (SPECT) estimates the provincial cerebral blood stream (rCBF). SPECT is basically used to assess blood stream and the level of fixation between blood vessel blood and brain tissue. Dopamine transporter radiotracers are also utilized with SPECT notwithstanding rCBF checking, and they might be clinically useful in separating between dementia types [27].

Specifically, the utilitarian imaging tests (MRI, PET, and SPECT scans) are pivotal from a clinical standpoint. With significant precision, they can distinguish individuals who are at a high risk of growing Promotion when they are in the MCI stage. The expectation of conversion from MCI to Promotion was shown to have sensitivity and specificity values of 89% and 85% for PET, 84% and 70% for SPECT, and 73% and 81% for MRI, as per a meta-analysis by Yuan et al. that comprised 24 trials with a sum of 1112 patients [35]. The distinction among Promotion and MCI has been successfully made by these imaging tests. Conversely, as individuals age, PET scans uncover bigger levels of amyloid (A+) positivity; nonetheless, this does not always infer cognitive decline or other cognitive disorders. As a result, individuals with presymptomatic disorders preceding MCI can't be consistently recognized using the visual translation of structural pictures [28].

3.2. High Invasive Biomarkers

The Public Institute on Maturing Alzheimer's Association has suggested the accompanying β amyloid deposition, pathologic tau, and neurodegeneration (ATN) recommendations for Promotion diagnosis that incorporate both CSF and imaging indicators [29]. The precision of perplexing Promotion diagnoses and prognoses is increased when it are joined to picture and CSF biomarkers. Because it is the 42-long amino corrosive (peptide) type of Aβ in brain tissue and the dominating biomarker connected with Promotion illness, the biomarker connected with Aβ in CSF is known as (Aβ42). Its level in CSF has a negative relationship with the amount of Aβ plaques in brain tissue, implying that the more Aβ plaques seen on PET scans, the lower the quantities of Aβ42 in the CSF. The risk progression from presymptomatic to MCI or from MCI to Promotion is connected to the proportion of Aβ42/Aβ40.

A protein called tau is present in the brain's neuronal axons. Promotion is connected to elevated degrees of both aggregate and p-tau in CSF. elevated levels of absolute tau and p-tau in the CSF suggest that the brain tissue neurons are secreting these substances, perhaps in response to uplifted Aβ plaques. Hyper-phosphorylated tau proteins are alluded to as P-tau. P-tau biomarkers come in three distinct varieties: P-tau181, P-tau217, and P-tau231. With regards to separating Promotion from non-Advertisement tau pathology or distinguishing the course of Advertisement through distinct phases, each is more useful in a specific scenario. The level of neurodegeneration might be anticipated using a biomarker for complete tau in the CSF. Neurofibrillary tangles made by tau accumulation impede synaptic transmission mechanisms and legitimate brain plasticity.

4. NOVEL NON-INVASIVE AND MINIMALLY INVASIVE BIOMARKERS

The multifaceted design of the formative processes for Promotion necessitates the discovery of biomarkers that work with the early diagnosis and headway of the illness. In any case, brain imaging and CSF biomarkers need invasive procedures for diagnosis. As a result, a precise and painless biomarker is expected to classify the phases of Promotion and the Promotion spectrum.

4.1. Non-Invasive Biomarkers

Electrical impulses are used by neurons to impart and complete the entirety of their operations. The EEG [30] records this electrical action using minuscule electrodes applied to the scalp, presenting electrical impulses as waves. A general slowing of the EEG, remembering a decrease for higher recurrence waves like gamma, is much of the time seen in Promotion patients. These EEG traits might be interesting applicant biomarkers of Promotion, as shown by the power spectrum, intricacy, and synchronization characteristics of EEG waveforms in Promotion patients that contrast significantly from those of ordinary matured individuals [31] [32]. The investigation of microvascular alterations in the retina by OCT and OCTA methods is another captivating biomarker. Its establishment is the immediate association between the eyes and the brain. Harm to the retina's neuronal microstructure and microvascular network has been shown in Promotion, MCI, and, surprisingly, preclinical Promotion, as per a new research [33]. Aβ and tau deposition are two examples of biochemical pathways that are changed in the retina during illnesses, as shown by studies of human and creature models of Promotion [34].

Consequently, EEG approaches with body fluid biomarkers might give a more exact expectation of Promotion status since they are harmless and distinct from most of other biomarkers utilized by other clinical-stage biotech businesses [35].

4.2. Minimally Invasive Biomarkers

Notwithstanding the CSF, other biomarkers for Alzheimer's disease are being discovered in the pee, saliva, and blood. For instance, 19 center point proteins shown a prescient limit of clinical Promotion order when hundreds of proteins in blood plasma were studied to foresee Advertisement [36]. Along these lines, the researchers took a gander at hundreds of distinct metabolites present in saliva to see which ones might foresee the presence of Promotion. This study demonstrated the capacity of salivary metabolite markers to distinguish between Promotion, presymptomatic (PP), and MCI patients. The metabolite markers glucosylgalactosyl, hydroxylysine — H2O, and glutamine-carnitine were used to distinguish Promotion and PP patients (AUC = 1.000, AUC = 1.000 with 100 percent sensitivity and 100 percent specificity in the discovery phase (DP) and approval phase (VP)). Metabolite indicators of alanyl-phenylalanine and phenylalanyl-proline (DP: AUC = 0.779; VP: AUC = 0.889) were the most compelling in separating between the MCI and Promotion groups. Besides, we had the option to separate Promotion from PP and MCI with high diagnostic execution (AUC > 0.8) by utilizing positively approved metabolites [37].

Furthermore, it has been shown that Promotion specific alterations in quality expression result in the Early Onset Alzheimer's Board. 45-90% of early Promotion patients might be recognized by three genes (the Apo E genotype, PSEN1, and PSEN2) [38]. Presently, the U.S. Food and Medication Administration has not approved any of these tests. The test is predicated on the exact and solid assurance of the ApoE genotype and the Aβ42/40 proportion (Aβ 42/40) in blood samples. In an alternate research, senile plaques and neurofibrillary alterations in the brain were connected to lactoferrin LF, a significant antimicrobial peptide in saliva. As a result, LF anticipates serving as an exceptionally precise and sensitive biomarker for the diagnosis of Promotion [39]. The Promotion continuum might be distinguished and classified using extra enzymes, hormones, or brain-secreted exosomal contents, such as proteins, lipids, and different RNA species present in blood or saliva. Furthermore, it has been shown that measurement errors might arise across institutions, in any event, when biomarkers are taken from the same populace sample [40].

For the painless or negligibly invasive early ID of Promotion, there isn't a traditional clinical treatment. The scientific local area is looking on logical techniques to incorporate this information as a result. The sections that follow give an outline of AI (ML) and man-made reasoning (artificial intelligence) for integrative information analysis.

Table 1: The reviews of authors' studies

Author	Method	Sample	Description
Jung, W.; Jun, E.; Suk, H.I.[41]	Deep recurrent model	personalized forecasting of the course of Alzheimer's illness	used a deep recurrent model to forecast the course of Alzheimer's illness in a tailored manner.
Tseng, W.I.; Hsu, Y.C.; Kao, T.W.[42]	Brain age difference	The difference in baseline brain age predicts Changes in Clinical Dementia Ratings	looked at how well the baseline brain age difference predicted changes in the Clinical Dementia Rating.
Liu, Y.; Yan, Z.[43]	Combined deep learning and lattice Boltzmann model	Hippocampal segmentation in MRI	created a lattice Boltzmann model with deep learning integrated for precise MRI hippocampal segmentation.
Leuzy, A.; Smith, R.; Cullen, N.C.; [44]	Biomarker-based prediction	Predicting longitudinal tau PET in Alzheimer's disease	suggested using biomarkers to predict longitudinal tau PET in Alzheimer's disease.
Palmqvist, S.; Tideman, P.; Cullen, N.; [45]	Plasma phospho-tau combined with other accessible measures	Future Alzheimer's disease dementia prognosis	investigated the use of plasma phospho-tau and other readily available metrics to forecast the onset of Alzheimer's disease dementia in the future.
Akenine, U.; Thunborg, C.; Kivipelto, M.; Fallahpour, M. [46]	Qualitative study	Experiences with taking part in a preventative trial	conducted a qualitative investigation to learn about the experiences of prodromal Alzheimer's disease participants in preventative trials.

5. CONCLUSION

Alzheimer's disease (AD) must be detected early in order to improve patient outcomes and lessen the strain on healthcare systems. Due to the shortcomings of traditional diagnostic techniques, new biomarkers and early detection strategies are being investigated [47]. Tests of episodic memory, subjective memory complaints, late-onset depression, and speech analysis show potential as non-invasive methods to detect AD patients. Although they are invasive, brain imaging techniques and CSF analysis are still useful for identifying AD-related disease [48]. The accessibility and use of novel non-invasive and minimally invasive biomarkers, such blood/saliva/urine biomarkers, ocular imaging methods, and EEG, may be advantageous [49]. [50]. However, in order to guarantee their accuracy and dependability across a range of populations, standardization and validation are necessary. Technological developments in AI and ML show potential for merging multimodal data and offering customized AD progression prediction. To further develop and evaluate these techniques and eventually provide more effective ways for early identification and intervention in AD, collaborative efforts are required.

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