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The Early Confirmation of Alzheimer's Disease using Internet Sources

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Abstract **- Alzheimer Disease (AD) is one of the common forms of dementia which is an irreversible neurodegenerative progressive disorder of the brain which affects the elderly population above the age of 65. Alzheimer is a brain disease that causes problems with memory, thinking and behaviour. It is severe enough to interfere with daily activities. Alzheimer symptoms are characterized by memory loss that affects day-to-day function, difficulty performing familiar tasks, problems with language, disorientation of time and place, poor or decreased judgment, problems with abstract thinking, misplacing things, changes in mood and behaviour, changes in personality and loss of initiative. There are different types of tests associated with AD such as neuropsychological tests, laboratory tests and various imaging modalities for the early diagnosis of AD. Although these tests are available, they are inadequate for the definite diagnosis of the disease. In this paper we focus on the databases related to AD such as ADNI (Alzheimer's Disease Neuroimaging Initiative), TREAD (Trajectory-Related Early Alzheimer's Database), CAMD (Coalition Against Major Diseases), and NAAC(National Alzheimer's Coordinating Center). The use of these internet sources, soft computing techniques and image analysis from the different imaging modalities in an efficient way for making a definite diagnosis and early confirmation of AD. Our aim is to predict the early diagnosis in a reliable manner such that to combine the values of different tests with the help of soft computing techniques to develop software tool for a definite diagnosis.**

Keywords **: Alzheimer Disease, ADNI, TREAD, CAMD and NAAC, Soft Computing techniques, image analysis.**

I. INTRODUCTION

Alzheimer's disease (AD) is an age related neuronal disorder of the brain that leads to memory loss and impairs the ability to perform routine functions as well [1, 2]. Alzheimer's disease was discovered in 1906 by Alois Alzheimer, a German neurologist and psychiatrist. In 2001, eleven million people suffered from Alzheimer's disease worldwide. At present nearly 36 (35.6) million people are believed to be living with Alzheimer's disease or other dementias, increasing to nearly 66 (65.7) million by 2030 and more than 115 (115.4) million by 2050[3]. The number of people with dementia will double by 2030, and more than triple by 2050[4]. The progression of the disease can be categorized in four different stages. The first stage is known as Mild Cognitive Impairment (MCI), and corresponds to a variety of symptoms (most commonly amnesia) which do not significantly alter daily life. Between 6 and 25% of people affected with MCI progress to AD every year. The next stages of Alzheimer's disease (Mild and Moderate AD) are characterized by increasing cognitive deficits, and decreasing independence, culminating in the patient's complete dependence on caregivers and a complete deterioration of personality (Severe AD) [5]. Alzheimer's disease is the sixth-leading cause of death and is 70% prevalent in all cases of dementia [6]. According to another report every 71 sec, someone develops Alzheimer's disease and the rate doubles roughly every 10 years after age 65 [7]. Alzheimer's disease is one of the underlying causes of dementia. Dementia is the term used to indicate impaired brain functions and encompass symptoms like memory loss, confusion, difficulty in performing routine tasks, loss of intellectual functions and impaired judgment. But, this condition is a symptom of many underlying neurological disorders including Alzheimer's disease, vascular dementia (Strokes and TIA's), Dementia with Lewy Bodies (DBL), Parkinson's disease, Frontotemporal Dementia (FTD), Normal-Pressure Hydrocephalus (NPH) and Delirium or Depression. AD is the most prevalent underlying cause of dementia and is clinically evident when there is gradual loss of higher brain functions including change in behavior and mood. The symptoms may progress to disorientation and aphasia (difficulty in language), indicating cortical dysfunction, agnosia (impairment in recognizing object and people), apraxia (impaired motor function) and significant of all, memory impairment. With disease progression patients suffer disability and immobility as well. The brain of such patients shows gross cortical atrophy with compensatory ventricular enlargement.

The most well-known neuropathological hallmarks of AD are extraneuronal senile plaques and intraneuronal neurofibrillary tangles (NFTs). Neurofibrillary tangles are filamentous bundles in cytoplasm of the neurons displacing or encompassing nucleus. In the pyramidal cells, they appear as 'flame' while in rounder cells they appear as 'globos tangles' [8]. Senile (neuritic) plaques present outside the neuron, appear as spherical bodies bearing dilated and tortuous neuritic processes around an amyloid beta core which contains some abnormal proteins like amyloid beta plaques which are derived through the processing of Amyloid Precursor Protein (APP) [8,9]. The aggregates of amyloid beta obtained from processing of APP are difficult to degrade which consequently activate inflammatory cascade that lead to oxidative injury and alterations in phosphorylation [8]. Familial causes or genetic mutations involved in disease pathology include

mutations on chromosomes 21, 14 and 1. Risk factors for AD are advanced age, lower intelligence, small head size, history of head trauma and female gender [10, 11].

Some of the earlier tests that were established for AD are Computed Tomography (CT) scans, structural Magnetic Resonance Imaging (MRI), and neuropsychological tests. CT scans were used to look for atrophy of the brain, and increased ventricle size. It was believed at first that cerebral atrophy was significantly greater in patients with AD than those without. However it was discovered later that healthy people also have cerebral atrophy. Patients with dementia may not have cerebral atrophy at least in the early stages of the disease. From these findings it was determined that it can be difficult to distinguish between a healthy elderly patient and a patient with dementia. Therefore, CT scans have been deemed as clinically unuseful in the primary confirmation of AD. After CT was discredited, questions were raised about using structural MRI performed a study to evaluate "predictive models of progression from amnestic MCI (mild cognitive impairment) to AD to assess the added benefit of structural MRI data compared to clinical measures alone. Structural MRI measures the "medial temporal lobe structures, whole brain volumes, and ventricular volumes. This turned out similar to the CT scans that were done. It became hard to distinguish between AD patient's brain atrophy and healthy patient's brain atrophy. Though we didn't find MRI structural measures, compared to cognitive measures, to be necessary for predicting AD in subjects with moderate degrees of MCI, this doesn't necessarily repudiate the utility of anatomic MRI as a potential biomarker for AD. Therefore MRI can be helpful in differentiating between MCI and AD [12]. In addition, PET uses biochemical means of acquiring images rather than structural information. "PET technology involves the detection of photons by a camera-like device that records the levels of radioactivity originating from given points in space and time. Positron emitting radioisotopes are used to generate the radioactivity"[13]. PET scan measures different compounds in the brain, in the case of AD; PET is used to measure fluorodeoxyglucose (FDG). FDG can compete with glucose for absorption and metabolism in neurons. With dementia the neurons intake of glucose and FDG becomes impaired. " By highlighting regions of decreased FDG uptake, PET can theoretically aid in the diagnosis of dementia, even in the absence of the gross structural damage detected by other imaging techniques such as CT or magnetic resonance imaging"[13].Some studies have been conducted to examine patients that are deemed amyloid positive or amyloid negative. Amyloid positive patients are said to be dominant carriers of AD, while amyloid negative patients are not performed this kind of study and they found [14],"amyloid positive subjects with mild cognitive impairment were much more likely to progress toa clinical diagnosis of Alzheimer's disease than amyloid negative subjects with mild cognitive impairment" (p. 3340). PET has been used extensively to study AD, and it is evolving into an effective tool for early diagnosis. PET has been used to detect people at risk for AD even before the symptoms start. PET is a very expensive scan to perform althoughhas been the most useful as far as providing visual images in the detection of AD. There are some new advances in technology that can not only detect AD, but possibly explain the symptoms and how the disease works.

Neuropsychological tests are used to determine the specific type and level of cognitive impairment that the patient has conducted a study using various types of neuropsychological tests. A few of them that were used include, "Rey Auditory Verbal Learning Test, category fluency, Trial Making Test parts A and B, Digit Symbol Substitution Test, Digit Span forward and backward, and the Clock Drawing task" [15].

All of these tests help to show the memory recall of a patient and the possible areas where the patient may be deficient. Using these tests can be helpful to determine the types of treatment plans that can be used, however neuropsychological tests alone are not helpful in detecting early AD. Trials were then conducted combining neuropsychological tests with clinical tests and various imaging modalities. For an effective and early diagnosis of AD, a population based study is necessary and required, which gives an idea about the various tests involved in determining AD. In this paper we uses different sources from internet such as ADNI, TREAD, CAMD and NAAC for determining the sensitive disease progression changes in the affecting areas related to Alzheimer's Disease with the help of clinical trials and implementing the sensitive changes with the help of image analysis and soft computing techniques.

II. ALZHEIMER DISEASE NEUROIMAGING INITIATIVE (ADNI)

The Alzheimer's disease Neuroimaging Initiative (ADNI) unites researchers with study data as they work to define the progression of Alzheimer's disease. ADNI researchers collect, validate and utilize data such as MRI and PET images, genetics, cognitive tests, CSF and blood biomarkers as predictors for the disease. Data from the North American ADNI's study participants, including Alzheimer's disease patients, mild cognitive impairment subjects and elderly controls. Alzheimer's disease (AD) affects almost 50% of those over the age of 85 and is the sixth leading cause of death in the US. Since 2005, the longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI) has been validating the use of biomarkers including blood tests, tests of cerebrospinal fluid, and MRI/ PET imaging for Alzheimer's disease (AD) clinical trials and diagnosis [16].ADNI also maintains an unprecedented data access policy intended to encourage new investigation and to increase the pace of discovery in the race to prevent, treat, and one day cure AD. All data is made available without embargo. Armed with better knowledge of the first indications of AD from ADNI and other studies, researchers are beginning to test potential therapies at the earliest stages feasible when there may the greatest promise for slowing

down progression of this devastating disease. ADNI is a global research effort that actively supports the investigation and development of treatments that slow or stop the progression of AD. This multisite, longitudinal study assesses clinical, imaging, genetic and biospecimen biomarkers through the process of normal aging to early mild cognitive impairment (EMCI), to late mild cognitive impairment (LMCI), to dementia or AD. With established, standardized methods for imaging and biomarker collection and analysis, ADNI facilitates a way for scientists to conduct cohesive research and share compatible data with other researchers around the world [16].The ADNI study has three phases: ADNI1, ADNI GO and ADNI2. New participants were recruited across North America during each phase of the study and agreed to complete a variety of imaging and clinical assessments. Participants are followed and reassessed over time to track the pathology of the disease as it progresses.

A. ADNI OR ADNI1

This is a non-randomized natural history non-treatment study in which a total of 800 subjects including 200 normal controls, 400 individuals with MCI, and 200 subjects with mild AD will be recruited at approximately 50 sites in the United States and Canada for longitudinal follow up. The major goals of the ADNI are to develop improved methods which will lead to uniform standards for acquiring longitudinal, multi-site MRI and PET data on patients with Alzheimer's disease (AD), mild cognitive impairment (MCI), and elderly controls, acquire a generally accessible data repository which describes longitudinal changes in brain structure and metabolism. In parallel, acquire clinical cognitive and biomarker data for validation of imaging surrogates; develop methods which will provide maximum power to determine treatment effects in trials involving these patients, test a series of hypotheses based on the clinical and biomarker data as outlined in the statistical analysis section. The enrolled subjects will be between 55-90 (inclusive) years of age ,have a study partner able to provide an independent evaluation of functioning, and will speak either English or Spanish. All subjects must be willing and able to undergo all test procedures including neuroimaging and agree to longitudinal follow up. Between twenty and fifty percent must be willing to undergo two lumbar punctures. Specific psychoactive medications will be excluded. General inclusion/exclusion criteria of ADNI are as follows in Table1:

TABLE 1 INCLUSION/EXCLUSION CRITERIA OF ADNI (SOURCE: WWW.ADNI-INFO.ORG)

1	Normal subjects: MMSE scores between 24-30 (inclusive), a CDR of 0, non-depressed, non-MCI, and nondemented
2	MCI subjects: MMSE scores between 24-30 (inclusive), a memory complaint, have objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.
3	Mild AD: MMSE scores between 20-26 (inclusive), CDR of 0.5 or 1.0, and meets NINCDS/ADRDA criteria for probable AD.

B.ADNI-GO

This is a non-randomized natural history non-treatment study in which 200 newly enrolled subjects from approximately 50 sites from the United States and Canada and approximately 450-500 subjects will be followed from the original ADNI study. The major goals of ADNI-GO are to, define and characterize the stage of the AD spectrum that precedes MCI as currently enrolled in ADNI1 (late MCI or LMCI) by enrolling 200 subjects in the mildest symptomatic phase of AD, early amnestic MCI (EMCI, defined more specifically below); perform F18 amyloid imaging (18F-AV-45) on the CN and LMCI subjects from ADNI1 (including those who had C-11 PIB) and the newly enrolled EMCI subjects. FDG PET will also be performed in association with F18 amyloid imaging. This establishes a national network for F18 amyloid imaging, and will test hypotheses concerning the prevalence and severity of brain amyloid accumulation and its relationship to current and previous changes of clinical state, MRI, FDG-PET, CSF and plasma biomarkers from ADNI1; define and characterize the stage of the AD spectrum that precedes MCI as currently enrolled in ADNI1 (late MCI or LMCI) by enrolling 200 subjects in the mildest symptomatic phase of AD, early amnestic MCI (EMCI, defined more specifically below); perform F18 amyloid imaging (18F-AV-45) on the CN and LMCI subjects from ADNI1 (including those who had C-11 PIB) and the newly enrolled EMCI subjects. FDG PET will also be performed in association with F18 amyloid imaging. This establishes a national network for F18 amyloid imaging, and will test hypotheses concerning the prevalence and severity of brain amyloid accumulation and its relationship to current and previous changes of clinical state, MRI, FDG-PET, CSF and plasma biomarkers from ADNI1. The newly enrolled subjects will be between 55-90 (inclusive) years of age, have a study partner able to provide an independent evaluation of functioning, and will speak either English or Spanish. All subjects must be willing and

able to undergo all test procedures including neuroimaging and agree to longitudinal follow up. 100% of the newly recruited EMCI subjects must be willing to undergo at least one lumbar puncture at baseline. Specific psychoactive medications will be excluded. General inclusion/exclusion criteria of ADNI-GO are as follows in Table2:

TABLE 2 INCLUSION/EXCLUSION CRITERIA OF ADNI-GO (SOURCE: WWW.ADNI-INFO.ORG)

EMCI Subject Inclusion Criteria:	MMSE scores between 24-30 (inclusive), a memory complaint (reported by subject or informant), must have objective memory loss measured by education adjusted scores on delayed recall of one paragraph from Wechsler Memory Scale Logical Memory II (between approximately 0.5 and 1.5 SD below the mean of Cognitively Normal), a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.
Follow-up Subject Inclusion Criteria:	In order to meet inclusion for follow-up these subjects must have been originally diagnosed as either Mild Cognitive Impairment (MCI) or Cognitively Normal (CN), and be willing and able to continue to participate. Subjects will be asked to continue in the trial even if a diagnostic conversion occurs.
Exclusion for amyloid imaging with 18F-AV-45:	Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the subject in any given year would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.

C.ADNI2

This is a non-randomized natural history non-treatment study where 550 newly enrolled subjects (150 CN, 100 EMCI, 150 LMCI, 150 mild AD) from approximately 55 sites from the United States and Canada, approximately 450-500 CN and LMCI subjects will be followed from the original ADNI study and approximately 200 EMCI subjects will be followed from the ADNI-GO study. The major goals of ADNI2 are to determine the relationships among clinical, imaging, genetic, and biochemical biomarker characteristics of the entire spectrum of Alzheimer's Disease (AD), as the pathology evolves from normal aging through very mild symptoms, to mild cognitive impairment (MCI), to dementia; inform the neuroscience of AD, identify diagnostic and prognostic markers, identify outcome measures that can be used in clinical trials, and help develop the most effective clinical trial scenarios; develop improved methods which will lead to uniform standards for acquiring longitudinal multi-site MRI and PET data on patients with AD, MCI, and elderly controls; perform longitudinal clinical, cognitive, MRI, PET (18F-AV-45 and FDG), and blood and CSF biomarker studies on 550 newly enrolled subjects in four diagnostic categories – cognitively normal (CN), early MCI (EMCI), late MCI (LMCI), and mild AD. Continue these longitudinal studies for approximately 500 LMCI and Cognitively Normal subjects from ADNI1 and approximately 200 EMCI subjects from ADNI-GO for an additional 5 years [16]. The newly enrolled subjects will be between 55-90 (inclusive) years of age, have a reliable study partner able to provide an independent evaluation of functioning, and will speak either English or Spanish. Specific psychoactive medications will be excluded. Additional inclusion/exclusion criteria of ADNI2 are as follows in Table 3:

TABLE 3 INCLUSION/EXCLUSION CRITERIA OF ADNI2 (SOURCE: WWW.ADNI-INFO.ORG)

Cognitively Normal Subjects:	MMSE scores between 24-30 (inclusive), a CDR of 0, non-depressed, non-MCI, and non-demented.
EMCI Subjects:	MMSE scores between 24-30 (inclusive), a subjective memory concern reported by subject, informant, or clinician, objective memory loss measured by education adjusted scores on delayed recall of one paragraph from Wechsler Memory Scale Logical Memory II (≥16 years: 9-11; 8-15 years: 5-9; 0-7 years: 3-6), a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.
LMCI Subjects::	MMSE scores between 24-30 (inclusive), a subjective memory concern reported by subject, informant, or clinician, objective memory loss measured by education adjusted scores on delayed recall of one paragraph from Wechsler Memory Scale Logical Memory II (≥16 years: ≤8; 8-15 years: ≤4; 0-7 years: ≤2), a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.

Mild AD Subjects:	MMSE scores between 20-26 (inclusive), a CDR of 0.5 or 1.0, and meets NINCDS/ADRDA criteria for probable AD.
Follow-up Subject Inclusion Criteria:	In order to meet inclusion for follow-up these subjects must have been originally diagnosed as either Mild Cognitive Impairment (MCI, early or late) or Cognitively Normal (CN), and be willing and able to continue to participate. Subjects will be asked to continue in the trial even if a diagnostic conversion occurs or they are no longer willing/able to continue with neuroimaging or LP procedures.
Exclusion for amyloid imaging with 18F-AV-45:	Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the subject in any given year would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.

All subjects will have clinical/cognitive assessments, biomarker and genetic sample collection, and imaging. A reduced battery of tests is allowable if the subject is not able/willing to complete the full battery after the participant's original Baseline Visit. All MRI and PET scans will be rapidly assessed for quality so that subjects may be rescanned if necessary. All clinical data will be collected, monitored, and stored by the Coordinating Center at University California San Diego. University of Pennsylvania will collect biomarker samples and NCRAD will collect genetic samples. The table 4 below summarizes the North American ADNI study target participant numbers, as well as the types of data taken at the different phases [16]

TABLE 4 SUMMARY OF ADNI STUDY (SOURCE: WWW.ADNI-INFO.ORG)

	NORMAL	EMCI	MCI	LMCI	AD	MRI	fMRI	DTI	FDG	AV45	PIB	BIOSAMPLE
ADNI 1	200	_	400	_	200	*			*		*	*
ADNI GO	↓	200	↓	_	_	*	*	*	*	*		*
ADNI 2	150	150	↓	150	200	*	*	*	*	*		*

III. TRAJECTORY-RELATED EARLY ALZHEIMER'S DATABASE (TREAD)

The overall aim of this research is to help detect the subtle declines in memory that occur in people with very early Alzheimer's disease (AD) in order find suitable volunteers for trials of promising treatments. We will establish a database for recruitment into new and promising treatment trials. Alzheimer's disease is the most common cause of dementia. AD is increasingly common as our population ages, and a hallmark is early decline in memory, which can be detected 5-10 years prior to severe memory problems using computerized memory testing. This research will use computer tests of memory and thinking developed in Melbourne that can be done over the internet and repeated periodically (e.g. monthly for 6 months, and then 3 monthly) to see if a person's memory is getting worse compared to their own baseline performance. This is a very sensitive way of detecting decline in memory and to identify people who should be offered further evaluation for possible causes, one of which is Alzheimer's disease. If evaluation suggests AD as the cause, we aim to offer participation in separate trials of promising new treatments. Participants in this study should have ready access to a computer that is connected to the internet, and be sufficiently skilful with that computer to be able to open a web browser and then follow the simple instructions of the test themselves. They should also live or be able to visit clinics in the Greater Melbourne area since they will be offered evaluation at a Melbourne clinic if decline in their memory is detected. The study will use computer tests including one developed by the Melbourne-based company CogState Ltd. The CogState test uses playing-cards and simple keyboard responses to assess speed and accuracy, which are direct measures of a person's ability to think clearly and quickly. It is designed to be easy to use and brief, taking about 15-20 minutes at most to complete all tasks. There is a practice test to familiarize you with what's required. The practice test does not keep score.

Then there is a scored test which would be used as the baseline for future comparisons. The test is started by clicking a web page link, runs itself interactively and when finished the results are sent to the study's secure database and analysed automatically. If you agree to participate in this research, you will be asked to do the computer testing every 1-3 months over at least 1-3 years. Initial testing would be at about monthly intervals for 6 months and then 3 monthly intervals. Most participants

are likely to show no significant decline in test results, but about 10% (based on our prior studies) may show decline in memory. In addition, it's possible that some participants with symptoms or even early dementia may not decline on the tasks used in this study. However, it is important to be aware that it's therefore possible that you will show decline in memory. We ask you to think carefully about whether you would like to know this information since you should not participate if you are unwilling to face this possibility at this time. In addition, a decline on the computer tests does not necessarily mean a person will get dementia or Alzheimer's disease, because there are many other possible reasons. If decline is found, it is important to consider undergoing a doctor's evaluation to seek identifiable causes of the decline. It would be your decision whether to undergo such evaluation and if so, by whom, whether by your own general practitioner (GP) or a Memory Clinic (which would liaise with your GP). Thus, at the start of the study, we would like you to nominate a preferred general practitioner (GP) to contact if necessary. The study is being conducted by the Florey Institute of Neuroscience and Mental Health (FINMH), with Principal Investigator, A/Prof David Darby, assisted by Associate Investigator Dr Amy Brodtmann. Funding is through the FINMH. However, there is a potential conflict of interest of which you should be aware. The Principal Investigator, A/Prof Darby, is a Founder, former director, and currently consultant and substantial shareholder of CogState Ltd, which is an ASX listed public company which supervises the commercial development of some of the cognitive testing software [17].

IV. CRITICAL PATH INSTITUTE (C-PATH) ONLINE DATA REPOSITORY (CODR): COALITION AGAINST MAJOR DISEASES (CAMD) ALZHEIMER'S DISEASE DATABASE

The Critical Path Institute (C-Path), in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution, has formed the Coalition Against Major Diseases (CAMD). Members include 6 non profit groups representing patients' interests, 15 leading pharmaceutical companies, the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA), 2 institutes of the National Institutes of Health (NIH)—the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS)—and representatives from academia. The coalition's purpose is to transform the drug development paradigm for neurodegenerative diseases and serve as a model for other major diseases.In 2004, the FDA's Critical Path Initiative identified neuropsychiatric diseases and disease models as priority areas of active research opportunities.2 The work of the coalition will focus on member companies' sharing of precompetitive data, which may include data from placebo groups from clinical trials not submitted as part of a New Drug Application, disease models, and/or protocol elements. In addition, industry will contribute scientific expertise that will lead to improved knowledge across disciplines; an important component in the development of treatments for Parkinson's and Alzheimer's diseases. Improved management of existing knowledge will be aimed at qualifying for use in drug development, novel imaging or biochemical markers (here, both are referred to as biomarkers), and quantitative disease progression models. The CAMD will intentionally avoid using terms such as "valid" or "surrogate" to describe biomarkers. Instead, the coalition will seek to develop methods that are "qualified for use" based on a rigorous review of scientific data by scientists from industry, academia, and regulatory agencies. These "qualified" methods are expected to lead to an increased efficiency in decision making during the drug development process and to a reduction in drug failures during late phase testing. the database regarding is as follows: The database contains 6,500 patients across 24 clinical trials of AD and MCI, but is not limited to, demographic information, APOE4 genotype, concomitant medications and cognitive scales (MMSE and ADAS-Cog); all data has been remapped to a common data standard (CDISC SDTM v3.1.2) such that all the data can be analyzed across all studies; it is openly available to CAMD members, as well as to external qualified researchers who submit, and are approved for, a request for access; biomarker data of AD biomarkers (imaging, bio fluids, expanded genetics beyond ApoE status), Exact names of test drug candidates from sponsor companies and background therapies per individual case are not included. The Primary applications for the Alzheimer's disease C-Path Online Data Repository are characterizes the dynamics of the placebo-arm within clinical trials of AD and MCI, Serves as a tool for the development of modelling and simulation tools for AD clinical trials; and item level data of clinical scales is present allowing investigators to analyze sub-items for specific analyses. The data is mapped to the CDISC foundational and AD-specific Study Data Tabulation Model (SDTM). Knowledge of SDTM is required for effective use of the data. Information and training on SDTM training is available from CDISC: no SDTM training is provided within CODR. The data consists of 11 SDTM domains: Disposition (DS), Demographics (DM), Adverse Events (AE), Concomitant Medications (CM), Medical History (MH), Subject Characteristics (SC), Subject Visits (SV), Questionnaires (QS), Laboratory Tests (LB), Vital Signs (VS), and Supplemental Qualifier (SUPPQUAL) [18].

V. NATIONAL ALZHEIMER'S COORDINATING CENTER (NACC)

NACC serves as a repository for data collected at approximately 29 Alzheimer's Disease Centers (ADCs) throughout the United States. The ADCs conduct clinical and biomedical research on Alzheimer's disease and

related disorders. Centers enroll their study subjects in various ways, including referral from clinicians, self-referral by patients themselves or concerned family members, active recruitment through community organizations, and volunteers who wish to contribute to research on various types of dementia. Most centers also enrol volunteer control subjects. Study subjects at each center are best regarded as a case series, not necessarily representing all cases of disease in a defined population [19]. The three main data research sets available from NACC are summarized in the table 5 below. NACC also archives several other, more specialized data sets, as described below.

TABLE 5 MAIN DATA RESEARCH SETS AVAILABLE FROM NACC

	Minimum data set (MDS)	Uniform Data Set (UDS) (LONGITUDINAL)	Neuropathology Data Set (NP)
Years covered	1984 - 2005	Sept. 2005 - present	1984 - present
Study subjects	Enrollees followed at ADCs (with or without dementia)	Enrollees followed at ADCs (with or without dementia)	Subjects who underwent autopsy
Approx. # of subjects*	74,397	28,444	13,279
Approx. # of variables	67	725	85
Method of data collection	Mainly abstracted retroactively from ADC medical records	Collected prospectively by clinicians, neuropsychologists, and other ADC research personnel	Standardized neuropathology form, completed by neuropathologist
Time period covered for each subject	Mainly status on last ADC visit; some variables also capture initial-visit status	Initial visit and each annual follow-up visit, plus milestones such as death or dropout	Status of brain at autopsy
Topics covered (brief list)	Demographics, cognitive status, clinical dementia diagnosis, selected clinical manifestations, comorbid conditions, MMSE score, vital status, primary neuropathological diagnosis (if died and had brain autopsy)	Socio demographics on subject and informant, family history, dementia history, neurological exam findings, functional status, neuropsych-ological test results, clinical diagnosis, whether imaging testing done, ApoE genotype	Demographics, date of death, primary and secondary neuropathological diagnoses, presence/absence of neuropathological features of most major dementias, APOE genotype, brain weights

VI. IMPLEMENTATION USING SOFT COMPUTING TECHNIQUES

Soft computing differs from conventional (hard) computing in that, unlike hard computing, it is tolerant of imprecision, uncertainty, partial truth and approximation. In effect, the role model for soft computing is the human mind. The guiding principle of soft computing is: “Exploit the tolerance for imprecision, uncertainty, partial truth, and approximation to achieve tractability, robustness and low solution cost”. The clinical data may consists of missing , incorrect and sometimes incomplete values set so using soft computing is the better alternative to handle such data. The principal constituents of soft computing are fuzzy logic, neural computing, evolutionary computation and probabilistic reasoning. The principal constituent methodologies in soft computing are complementary rather than competitive. Fuzzy logic handles imprecision, neural computing deals with learning, evolutionary computation is for optimization and probabilistic reasoning handles uncertainty.

VII. CONCLUSION

There are a lot of clinical tests, drug therapies and diagnostic tools such as biomarkers and neuroimaging techniques are available for the diagnosis of Alzheimer’s disease. But the fact is that these techniques are inadequate for the definite diagnosis at the earlier stages. The different internet sources of Alzheimer disease patients discussed here gives a complete idea of how the disease can be predicted before the disease progresses and very much useful for creating computer operated software with the help of various soft computing techniques. From the above

understandings it is clear that a newly reliable and efficient method should be developed in order to diagnose the disease with the advanced biomedical engineering technology techniques which can be useful to a great extent for the early and definite diagnosis of the disease.

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