

Submission To:

**House of Representatives Standing Committee on Health and Ageing
Inquiry into Dementia: Early diagnosis, and Intervention**

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Summary

- Alzheimer's Disease (AD) and related causes of dementia are currently diagnosed late in the course of the illness.
- Australia is a leader in pioneering methods which can lead to early diagnosis. At the forefront is the Australian Imaging, Biomarker and Lifestyle (AIBL) study which will enable prognostic indications to be developed, possibly in the preclinical stages of AD.
- Australian researchers and their international collaborations are engaged in a process to standardize diagnostic categories of dementia using cognitive, neuroimaging, and biomarkers.
- Australia should follow the lead set by the US in developing a National Plan to address early diagnosis, prognosis and intervention for AD.

The Mental Health Research Institute (MHRI) is one of the major centers in Australia for research into Alzheimer's disease (AD), Parkinson's disease (major neurodegenerative diseases), depression and schizophrenia (major psychotic disorders). Current research on dementia at the Institute is focused on understanding the biological basis of these diseases and identifying methods for pre-symptomatic diagnosis of Alzheimer's disease and effective treatments. Alzheimer's disease is the most common form of dementia, affecting approximately 1 in 10 people aged over 75, and is projected to become one of the largest health issues affecting our aging population. Apart from the devastating impact of this disease on individuals, their families and friends and communities, the cost of caring for the incapacitated individuals is immense, both to the carers and to the aged and health care systems. Several aging studies conducted both in Australia and abroad show that dementia is not a part of the normal aging process, and thus must be investigated as a treatable disease state which has clear pathological features.

While dementia covers a range of diseases that involve memory loss and cognitive impairment, a majority of dementia cases are caused by Alzheimer's disease, which is characterized by both distinctive cognitive and pathological features. Pathological features include significant loss of neurons and brain mass, and the formation of amyloid plaques and neurofibrillary tangles. In terms of cognition the prominent features include significant memory impairment, loss of decision making abilities and behavioral/personality changes. These deficits eventually become so severe that individuals can no longer care for themselves and require constant supervision and assistance with the most basic activities of daily living. This is well documented elsewhere and is not the focus of this submission.

Current state of diagnosis, prognosis and intervention for Alzheimer's disease.

Currently, the best case scenario for the diagnosis of Alzheimer's disease is to be diagnosed in a "timely" fashion, i.e. when symptoms are apparent, yet are not severe enough to cause significant issues to the individual and their ability to live independently. Unfortunately, this does not occur very often, and in most cases Alzheimer's disease is not specifically diagnosed until significant impairment in cognition has occurred. This is partly because the only clinical method for the diagnosis of AD is based on cognitive function tests administered by specialist physicians or neuropsychologists, which are inherently insensitive to the early subtle changes in cognition that signal the beginning of the decline into Alzheimer's disease. This is clearly a limitation. It is not a straightforward process which can be administered by a general practitioner, nor is the process 100% accurate, leading to misdiagnosis and inappropriate treatments, such as anti-psychotics in the case of mis-diagnosis of Alzheimer's disease as depression. These and other factors lead to chronic rates of under-diagnosis or late diagnosis of these dementing diseases, which is widely concluded to be too late for effective intervention apart from limited pharmacological treatments to alleviate some of the symptoms of the disease.

A further limitation of the current approaches to Alzheimer's disease intervention are that they are ineffective at preventing or delaying the progression of the disease. In most cases the therapeutic interventions that are used to alleviate symptoms focus on improving the function of the remaining nerve cells through increasing the amount and stability of neurotransmitters. This does nothing to address the underlying cause of the synaptic loss and neuronal death, and hence is of limited use in preventing progression. As we do not have a good understanding of the basis of the synaptic loss

the development of drug based interventions is difficult. Other interventions such as diet and exercise are still under investigation, and have not yet been proven to have any significant beneficial effects on AD.

Australian Initiatives in Early diagnosis, prognosis, and intervention

As the Australian leader in Alzheimer's disease research, MHRI formed a consortium with CSIRO, Edith Cowan University, Austin Health and the National Ageing Research Institute in 2007 to create the Australian Imaging Biomarker and Lifestyle Study of Ageing (see attachment 1: Ellis et al 2009).

This 1100 person cohort in Perth and Melbourne has now been followed for more than three years, and its purpose is to answer fundamental questions of relevance to this Inquiry, specifically: what is the natural history of Alzheimer's disease in the Australian community? What lifestyle factors might be important for determining age at onset and rate of progression? What are the methods to improve early diagnosis and to give reliable indication of prognoses ("help people with dementia and their carers to plan for their futures")? What are the prospects for intervention, using either novel therapeutic strategies (drugs) or lifestyle modifications? How best to communicate with all stakeholders on the results of the AIBL Study?

AIBL has proven to be an immense success, with many insights into early diagnosis and intervention either achieved or close to fruition. More recently, the AIBL team and other partners have successfully formed the Cooperative Research Centre for Mental Health, a \$70m Commonwealth Government program over the next seven years which will assist AIBL in reaching its goals and utilize its technologies in other forms of dementia and cognitive impairment.

Recent developments for international cooperation in early diagnosis and intervention.

There have been two recent international events around Alzheimer's disease and the research that is conducted into investigating issues that we believe are relevant to this Inquiry. First is the recent Australian conference into standardization of the research aimed at identifying improved Alzheimer's disease early diagnosis. The second is the US Government's Department of Health and Human Services National Plan to Address Alzheimer's disease.

Research and standardization of AD (RASAD) conference.

In March 2012, AIBL hosted an international conference that aimed to develop a consensus between industrial and academic researchers, clinicians and regulatory authorities on the standardization and validation of imaging, biomarker, psychometric and lifestyle investigations worldwide. Several key conclusions and recommendations arose from the proceedings of the conference (see attachment 2: Carillo et al; In Preparation). The conference delegates agreed that significant progress in the development of surrogate markers for Alzheimer's disease had been achieved, but that the current accuracy of these markers was not sufficient to obtain diagnosis on an individual level. It was also concluded that these markers were most useful for enriching clinical cohorts with people who have increased potential for developing Alzheimer's disease, rather than as a diagnostic or prognostic tool. This is a critical point in the investigation of Alzheimer's disease treatments, as currently most clinical trials are conducted on cohorts with a very high proportion of individuals with late stage Alzheimer's disease, which is now widely considered to be difficult to treat.

The conference delegates agreed that continued progress towards a diagnostic or prognostic marker required increased research focused on the identification and characterization of new biomarkers, with particular attention paid to worldwide standardization of protocols and techniques. In addition, it was agreed that we still do not fully understand the biological basis for Alzheimer's disease, which may be hampering efforts to identify new potential markers of the disease.

Imaging techniques to diagnose AD were also discussed, including the use of structural magnetic resonance imaging and Pittsburgh compound B-positron emission tomography (PIB-PET) imaging. Both these techniques were concluded to have some clinical utility in Alzheimer's disease and dementia diagnosis, with PIB-PET able to observe pathologically associated changes in brain scans approximately 10-20 years prior to the onset of cognitive symptoms. It was also concluded that negative imaging scans should only raise questions in regard to a diagnosis of a particular disease and are not completely diagnostic, due to the lack of understanding of the cutoff for the detection of the pathological hallmarks of the disease. Unfortunately these imaging techniques are expensive, and were also concluded to be widely used only for clinical purposes in resource rich countries.

The key conclusion to come from this conference is that biomarker and imaging studies are advancing rapidly, and that there will come a time soon when we will be able to diagnose and

prognosticate on Alzheimer's disease prior to the onset of symptoms. The main concern raised in regard to this conclusion was that valid and accurate markers of the disease are needed but should be deployed with effective interventions to take advantage of this early diagnosis.

U.S. National Plan to address Alzheimer's disease.

Recently, the US department of Health and Human Services released a national plan to address Alzheimer's disease (Professor Colin L. Masters was invited to the launch at NIH as the Australian representative). This report states that the U.S government aims to eliminate the burden of Alzheimer's disease and lists five main goals to achieve this aim, which mostly apply to the terms of reference for this inquiry (see attachment 3, NPAAD 2012; <http://aspe.hhs.gov/daltcp/napa/NatPlan.shtml>).

The first goal, and one that we would argue is most important, is to **prevent and effectively treat Alzheimer's disease by 2025**. To achieve this goal, the report sets out several strategies primarily focused on developing a better understanding of the biological basis of Alzheimer's disease, including developing defined research priorities and milestones, expand research aimed at preventing and treating Alzheimer's disease, accelerating identification of early and pre-symptomatic states of the disease and facilitating the translation of the findings into public health and medical practice. These strategies recognize that current methods for diagnosis and treatment are inadequate to effectively identify and intervene in the disease progression, and that significant emphasis must be placed on understanding the basis of the disease to achieve the goal of both early diagnosis and effective intervention.

The second goal of the Plan addresses the third and fourth term of reference for this enquiry. **The goal is to enhance care quality and efficiency**, through several related actions. Quality of care can be increased by building a highly skilled aged healthcare workforce through targeted education and training programs and increased specialization in geriatric medicine among healthcare providers. The Plan recognizes the importance of timely and accurate diagnosis, and aims to improve these parameters through public engagement and administration of standardized assessments during regular health checks of aged individuals. The Plan also recognizes the importance of educating affected individuals, the families and friends of affected individuals and their physicians in the available support strategies, the steps to get the required support, and the long-term planning of future care requirements for the affected individual. In addition the plans

describes aiming to ease transitions between care providers, and provide coordinated care plans for affected individuals, while determining the most effective model for the care of these individuals.

The third goal also is relevant to the first, second and third terms of reference, and effectively states that the U.S. government aims **to expand the community supports provided to care-givers and people afflicted with Alzheimer's disease.** This overall goal covers a broad range of parameters. Initially the Plan aims to address the preparedness of care-givers to face the challenges of caring for an Alzheimer's disease patient through the development and delivery of education programs in both a physical and information technology based package. Part of this education package will focus on improving the awareness of long-term services that may be required during the later stages of Alzheimer's disease. This area of the plan also details strategies to assist care-givers in maintaining their own health and well-being while providing care by identifying areas where assistance is lacking, assessing care-giver well-being through various long-term service and support providers, and determining what interventions, such as respite care, can be utilized to improve care-giver wellbeing. Additionally, this goal also covers protecting the afflicted individuals, who are quite vulnerable to exploitation and abuse, and investigating the best methods of providing stable housing and living environments.

The fourth goal primarily aims **to inform the general public about diagnosis,** treatment and progression of the disease and is essentially an expanded education and public awareness campaign to reduce the misconceptions in regards to the early symptoms of the disease, and decrease the stigmatism and isolation that care givers of Alzheimer's disease patients regularly endure.

The fifth and final goal is to **regularly update the national plan** such that progress can continue. This goal recommends the formation of a department for overseeing the national plan and the development of processes for tracking progress and achievements.

These goals reflect the pathways that should be followed in regards to dealing with dementia and Alzheimer's disease: development of accurate diagnosis, support for prognosis research into interventions that provide effective treatment for the disease, identification of processes and educational interventions to to effectively support care-givers in the community and the development of public awareness of the problems which face us as a community. We would propose to the Standing Committee that Australia would do well to develop a similar National Action Plan.

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Attachments:

- 1) Ellis KA, Bush AI, Darby D, De Fazio D, Foster J, Hudson P, Lautenschlager NT, Lenzo N, Martins RN, Maruff P, Masters C, Milner A, Pike K, Rowe C, Savage G, Szoeki C, Taddei K, Villemagne V, Woodward M, Ames D and the AIBL Research Group. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *Int Psychogeriatr* 2009; 21: 672-687.
- 2) Carillo MC, Szoeki C, Masters CL, Rowe C, Ames D, O'Meara T, Macauley L, Milner A, Head R (Ellis K, Maruff P, Bain L). Research and standardization in Alzheimer's trials: Reaching international consensus. (In Preparation)
- 3) U.S. Department of Health and Human Services. National Plan to Address Alzheimer's Disease (NPAAD) - <http://aspe.hhs.gov/daltcp/napa/NatlPlan.shtml>, 2012.

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease

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¹⁵See Appendix 1

ABSTRACT

Background: The Australian Imaging, Biomarkers and Lifestyle (AIBL) flagship study of aging aimed to recruit 1000 individuals aged over 60 to assist with prospective research into Alzheimer's disease (AD). This paper describes the recruitment of the cohort and gives information about the study methodology, baseline demography, diagnoses, medical comorbidities, medication use, and cognitive function of the participants.

Methods: Volunteers underwent a screening interview, had comprehensive cognitive testing, gave 80 ml of blood, and completed health and lifestyle questionnaires. One quarter of the sample also underwent amyloid PET brain imaging with Pittsburgh compound B (PiB PET) and MRI brain imaging, and a subgroup of 10% had ActiGraph activity monitoring and body composition scanning.

Results: A total of 1166 volunteers were recruited, 54 of whom were excluded from further study due to comorbid disorders which could affect cognition or because of withdrawal of consent. Participants with AD (211) had neuropsychological profiles which were consistent with AD, and were more impaired than participants with mild cognitive impairment (133) or healthy controls (768), who performed within expected norms for age on neuropsychological testing. PiB PET scans were performed on 287 participants, 100 had DEXA scans and 91 participated in ActiGraph monitoring.

Conclusion: The participants comprising the AIBL cohort represent a group of highly motivated and well-characterized individuals who represent a unique resource for the study of AD. They will be reassessed at 18-month intervals in order to determine the predictive utility of various biomarkers, cognitive parameters and lifestyle factors as indicators of AD, and as predictors of future cognitive decline.

Key words: Alzheimer's disease, mild cognitive impairment, healthy controls, cohort study, longitudinal study, PiB PET imaging

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Introduction

The burgeoning global increase in the number of people with dementia from around 26 million in 2005 to over 80 million by 2040 (Ferri *et al.*, 2005) presents a public health challenge of unprecedented magnitude. However, disease modifying treatments with the potential to delay the onset of the clinical symptoms of Alzheimer's disease (AD) (the commonest cause of dementia) are in development. It is quite possible that one or more of these potential treatments will be found to have the capacity to delay the age at onset of AD in susceptible individuals (Ritchie *et al.*, 2007). In Australia, where the number of people affected by dementia is expected to triple from the current 234,000 (1% of the population) in 2009 to 731,000 (2.8% of the projected total population) by 2050, delaying the onset of AD by 5 years could nearly halve the total cost of dementia to society (Access Economics, 2005).

If safe and effective disease modifying therapies for AD emerge within the next decade (Ritchie *et al.*, 2007), it will be necessary to test whether these therapies are efficacious in preventing or delaying symptom emergence in those at high risk of developing AD. Although some risk factors, such as carrying an apolipoprotein E ϵ 4 (ApoE ϵ 4) allele, have been found to raise an individual's chance of developing AD, current knowledge does not permit us accurately to calculate the risk of an individual (as opposed to a population) developing AD at a particular time in the future. To identify an appropriate population in which preventative AD therapies could be trialed, we need to identify biomarkers that can predict reliably which individuals are likely to develop AD and over what time period this may occur.

Putative biomarkers for the future development of AD include the presence of brain amyloid in asymptomatic individuals detected by Positron Emission Tomography with Pittsburgh Compound B (PiB PET imaging) (Rowe *et al.*, 2007), levels of A β 42 amyloid and its precursors and metabolites in plasma, and the ratio of tau and A β 42 in the cerebrospinal fluid (CSF) (Takeda *et al.*, 2007). In order to determine how well these and other potential biomarkers may predict the risk and timing of AD incidence, it is necessary to examine cohorts of individuals who possess varying levels of AD risk. Furthermore, such groups need to be investigated and re-assessed prospectively over long periods of time in order to establish who will develop AD and when their symptoms will appear. It also would be of significant benefit to ascertain, in greater detail than is currently known, which health and lifestyle factors protect against

or contribute to the development of AD. The extent to which these factors confer an increased or decreased risk requires further investigation in order to clarify how much variance in the incidence of AD can be attributed to genetic endowment and how much to other factors, and how different causative and protective factors interact. Identification of such factors might permit early treatment and modification of risk factors to delay or defer the onset of irreversible disease.

To this end, the Australian Commonwealth Scientific Industrial and Research Organisation (CSIRO) formed a partnership in late 2005 with a number of leading researchers and research organizations located in the Australian cities of Melbourne and Perth (see Appendix 2). The aim was to assemble a cohort of individuals who could be assessed and followed at regular intervals and whose tissues, amyloid brain load, and lifestyle factors could be compared in relation to their cognitive function (especially with respect to the presence or absence of AD symptoms) and risk factors. Our initial objective was to develop a cohort of over 1000 individuals, at least 200 of whom would have a current diagnosis of AD, and to assess them at baseline and again after 18 months. We intended to look for biological differences between those with and without AD and then to follow the cohort for many years to determine which putative biomarkers, cognitive characteristics and health and lifestyle factors determine subsequent development of symptomatic AD. Further, we considered it was important to dichotomize apparently healthy individuals on the basis of whether they expressed concern about their subjective memory function, as there is disagreement in the literature as to whether such subjective memory complaints are, or are not, predictive of future cognitive decline (Jonker *et al.*, 2000; Glodzik-Sobanska *et al.*, 2007; Reisberg, 2007; Reisberg and Gauthier, 2008).

We hypothesized that retrospectively cross-referencing putative blood biomarkers with both longitudinal cognitive measures and the presence or absence of brain amyloid detected by PiB PET scanning would enable the identification of blood biomarkers which detect the Alzheimer's disease process prior to the emergence of clear cognitive symptoms. Further, we hypothesized that lifestyle factors, such as exercise and diet (Lautenschlager *et al.*, 2008), would be associated to some degree with cognitive outcome. The collaboration was launched at a media event in November 2006, which was used to appeal to volunteers aged 60 and over to assist with the research project. This paper describes the study methodology, including the assembly of the cohort, and reports the baseline characteristics of the participants in the Australian Imaging,

Biomarkers and Lifestyle flagship study of aging (AIBL study), including demography, medical history, neuropsychology and mood measures.

Methods

We sought to recruit and characterize 1000 individuals from the following groups:

1. At least 200 individuals with AD as defined by NINCDS-ADRDA criteria (McKhann *et al.*, 1984).
2. At least 100 individuals with mild cognitive impairment (MCI) – MCI is a clinical syndrome characterized by reduced cognitive performance (often involving memory), which represents a high risk state for the development of frank AD (Petersen *et al.*, 1999; Winblad *et al.*, 2004).
3. At least 700 healthy individuals without cognitive impairment. This group included:
 - a. volunteers with at least one copy of the ApoE ϵ 4 allele,
 - b. volunteers without a copy of the ApoE ϵ 4 allele,
 - c. volunteers who expressed subjective concern about their memory function (“memory complainers”; these individuals may belong to either group a or b above). Memory complaints were elicited by the response to the question: “Do you have difficulties with your memory?”

Allocation of individuals to one of the three diagnostic groups and exclusion of ineligible individuals was undertaken by a clinical review panel chaired by DA, details of which are outlined below. When individuals presented with a diagnosis of AD or MCI that had already been made by a treating clinician, this diagnosis was reviewed by the clinical review panel, in order to ensure that diagnoses were made in a consistent manner according to internationally agreed criteria.

The numbers to be recruited were in line with other similar international cohorts and were largely determined by available funding. It was agreed that recruitment would cease once each of the specific targets for each of the three diagnostic groups had been attained.

The AIBL study was approved by the institutional ethics committees of Austin Health, St Vincent’s Health, Hollywood Private Hospital and Edith Cowan University, and all volunteers gave written informed consent before participating in the study.

Telephone screening

Over 4000 individuals responded to a media appeal for volunteers, while others volunteered after their treating physician had informed them about the AIBL study. All AIBL volunteers underwent initial screening. The majority were

screened by telephone between December 2006 and February 2007, while a small number of volunteers completed screening on the day of their AIBL assessment. Questions included basic demographic data (age, sex, contact details), information about certain aspects of medical history (diagnosed dementia, schizophrenia, bipolar disorder, depression, Parkinson’s disease, cancer, cardiovascular disease including stroke, diabetes, alcohol intake), and whether they perceived any difficulty with their current memory function. The 15-item Geriatric Depression Scale (GDS-15) (Brink *et al.*, 1982; Yesavage *et al.*, 1982; Sheikh and Yesavage, 1986) was also completed. Individuals who volunteered to take part were excluded if they had a history of non-AD dementia, schizophrenia, bipolar disorder, significant current (but not past) depression (GDS score above 5/15), Parkinson’s disease, cancer (other than basal cell skin carcinoma) within the last two years, symptomatic stroke, uncontrolled diabetes, or current regular alcohol use exceeding two standard drinks per day for women or four per day for men.

Based on the screening interview, individuals who were suitable for participation were invited to attend for assessment. Assessments took place between late 2006 and August 2008. Individuals with diagnosed AD or MCI, and healthy individuals who were aged over 75 years, were the first participants invited for assessments. Baseline testing continued until the target of assessing 200 AD participants was reached, which took the total cohort size to 1166 participants.

Attendance for AIBL assessment

Assessments took place at three locations in Melbourne and at two locations in Perth, depending on whether the participants were to undergo brain imaging and where they lived. For a small number of participants (especially for some of those affected by AD), AIBL staff assessed them at home. Prior to assessment, detailed information about the study was sent to participants. Upon arrival, volunteers discussed the study in detail with a senior member of the research team before signing informed consent.

All assessments were conducted in the mornings, after an overnight fast. Weight, height, abdominal girth, sitting blood pressure and pulse were measured, followed by the drawing of 80 ml of blood. Participants were then provided with breakfast, followed by cognitive and mood assessments, as described below.

Cognitive and mood assessment

Cognitive and mood tests were performed by trained staff, most of whom were qualified

neuropsychologists. Some tests were selected on the basis of their internationally acknowledged utility and their ubiquity in the research literature (e.g. the Mini-mental State Examination (MMSE) and GDS). The tests comprising the neuropsychological battery were selected on the basis that together they covered the main domains of cognition that are affected by AD and other dementias. These tests were chosen so that results from our participants were comparable with those from other similar large studies, and all are internationally recognized as having good evidence of their reliability and validity. Readers who would like more information about our test battery are invited to contact the corresponding author by email.

The full battery comprised the MMSE (Folstein *et al.*, 1975), California Verbal Learning Test – Second edition (CVLT-II) (Delis *et al.*, 2000), Logical Memory I and II (WMS; Story A only) (Wechsler, 1945), D-KEFS verbal fluency (Delis *et al.*, 2001), 30-item Boston Naming Test (BNT) (Saxton *et al.*, 2000), Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), Digit Span and Digit Symbol-Coding subtests of the Wechsler Adult Intelligence Scale – Third edition (WAIS–III) (Wechsler, 1997), the Stroop task (Victoria version) (Strauss *et al.*, 2006), and the Rey Complex Figure Test (RCFT) (Meyers and Meyers, 1995). The length of the assessment typically ranged between one and two hours. Participants also completed the computerized CogState battery (www.cogstate.com) which took approximately 30 minutes to complete. The CogState battery consists of five initial tasks displaying playing-card stimuli. These include the Detection Task (reaction time task measuring psychomotor function), the Identification Task (choice reaction time task measuring visual attention), the One Card Learning Task (assessing visual recognition memory and attention), and the One-Back Task (assessing working memory and attention). For all tasks speed (reaction time in milliseconds) and accuracy (number of correct responses made) of each performance were recorded. The final task was the Continuous Paired Associate Learning Task (assessing associate learning and memory); accuracy of performance was calculated by totaling the number of errors made in each round of the task.

In addition to GDS scores obtained at screening, the Hospital Anxiety and Depression Scale (HADS) (Snaith and Zigmond, 1986; Zigmond and Snaith, 1983) was completed. For participants with a diagnosis of AD or MCI, an informant was asked to provide additional information about the functional performance of the research participant and to complete the Informant Questionnaire on Cognitive Decline (IQCODE) (Jorm and Jacomb, 1989).

Dementia severity was rated for all participants using the Clinical Dementia Rating scale (CDR) (Morris, 1993), on the basis of information obtained from cognitive testing, direct questioning of the participant, and information from an informant and/or from the participants' treating clinician (for those diagnosed with AD or MCI). This scale, which assesses six domains of function (memory, orientation, problem solving, home and hobbies, community affairs, self care) is scored according to a specific algorithm to indicate whether dementia is absent (CDR = 0), questionable (CDR = 0.5), mild (1), moderate (2) or severe (3). Moreover, because six domain scores ranging from 0 to 3 are generated on the CDR, it is possible to calculate a "sum of the boxes" score (ranging from 0 to 18).

Blood samples

Of the 80 ml of blood sample taken on arrival, 27 ml was forwarded to a clinical pathology laboratory (Melbourne Health in Melbourne, and PathWest Laboratory Medicine WA in Perth) for baseline testing, which included full blood examination, erythrocyte sedimentation rate, urea and electrolytes, creatinine, androgen levels, globulin levels, sex hormone binding globulin (SHBG), glomerular filtration rate, calcium, liver function tests, serum lipids, homocysteine, serum and red cell folate, B12, glucose, insulin, ceruloplasmin, ferritin/transferrin/iron, estradiol, luteinizing hormone, thyroid function (thyroid stimulating hormone, free thyroxine, free triiodothyronine), and prostate specific antigen (males only). One 0.5 ml tube of whole blood was forwarded for apolipoprotein E genotyping. Another 0.5 ml of whole blood was stored in liquid nitrogen. The remaining blood was fractionated into the following components: serum, plasma, platelets, red blood cell, white blood cell (in dH₂O) and white blood cell (in RNAlater, Ambion). These components were stored in liquid nitrogen in 92 aliquots (NUNC cryo-vials) which ranged in size from 0.25 ml to 1 ml. Stored blood samples were sourced from three different tube types: lithium-heparin tubes, EDTA tubes with added prostaglandin E1 (Sapphire Biosciences, 33.3 ng/ml), and serum tubes.

Medical history and medication use

All participants completed a detailed questionnaire regarding family medical history (including family history of psychiatric disorders, dementia, and other neurological illnesses), personal medical history, medication use and smoking, and questions about current and past alcohol and illicit drug use.

Brain imaging

Funding was available for 250 participants to undergo Magnetic Resonance Imaging (MRI) and PET imaging with Pittsburgh Compound B (PiB), an *in vivo* amyloid imaging agent. PiB imaging methodology has been described previously (Pike *et al.*, 2007). 3D T1 MPRAGE and a T2 turbospin echo and FLAIR sequence MRI was acquired for screening and co-registration with the PET images. PET standardized uptake value (SUV) data acquired 40–70 minutes post-PiB injection were summed and normalized to the cerebellar cortex SUV, resulting in a region to cerebellar ratio termed the SUV ratio (SUVR).

Health and lifestyle

All participants were asked to complete the International Physical Activity Questionnaire (IPAQ) (Craig *et al.*, 2003) and the Food Frequency Questionnaire (FFQ) (Hodge *et al.*, 2000). A subset of the Perth cohort had their physical activity recorded for seven days by a computerized ActiGraph monitor. A subgroup from Perth also underwent low dose radioactive (DEXA) scans to assess body composition (including fluid, bone, and adipose tissue).

Clinical review and the diagnosis of AD or MCI

Monthly clinical review panel meetings were conducted to discuss the baseline diagnostic classification for all participants with a diagnosis of AD or MCI, and for those who participated as healthy controls who required further investigation. This latter group included healthy participants who demonstrated any of the following: MMSE score <28/30, failure on the Logical Memory test (as per ADNI criteria), other evidence of possibly significant cognitive difficulty on neuropsychological testing, a CDR score of 0.5 or greater, a medical history suggestive of the presence of illnesses likely to impair cognitive function, an informant or personal history suggestive of impaired cognitive function, or who were consuming medications or other substances that could affect cognition. A consensus diagnosis was assigned for each such participant, which included consideration of diagnostic criteria (DSM-IV diagnosis (American Psychiatric Association, 1994) and ICD-10 diagnosis (World Health Organization, 1992)) and whether the subject violated any exclusion criterion. Where appropriate, ICD-10 dementia severity rating (World Health Organization, 1992), NINCDS-ADRDA AD diagnosis (probable or possible) and MCI classifications were applied. The clinical review panel comprised old age psychiatrists

(DA, NL), a neurologist (DD), a geriatrician (MW) and neuropsychologists (JF, KE, GS, KP, DDF). A quorum was formed by three members including at least one medically qualified and at least one psychologist member. The panel conferred monthly via telephone conference and most meetings were attended by five or more participants. All but two of these conferences were chaired by DA.

MCI diagnoses were made according to a protocol based on the criteria of Winblad *et al.* (2004) which are informed by the criteria of Petersen *et al.* (1999). Consistent with Winblad criteria, all participants classified with MCI had either personally, or through an informant, reported memory difficulties. Participants presenting with a clinical diagnosis of MCI (i.e. previously diagnosed by a clinician) were further required to demonstrate a score 1.5 SD or more below the age-adjusted mean on at least one neuropsychological task applied at the time of the AIBL assessment in order to be retained in the MCI category. Individuals who volunteered to take part as healthy controls had to fulfill the more stringent criterion of impairment on two or more cognitive tests at a level at least 1.5 SD below the age-adjusted mean, in addition to having reported memory difficulties, to be classified as MCI. The greater stringency applied to allocating individuals presenting as healthy controls (HCs) to the MCI category was decided upon after extensive discussion, and is justified by the acknowledged mutability of MCI diagnoses. Individuals were then characterized as amnesic or non-amnesic, and single or multi-domain subtypes of MCI, on the basis of the specific tests on which they had shown impaired performance. All participants with MCI manifested substantially intact activities of daily living and exhibited no clear evidence of significant impairment in their social or occupational functioning.

Statistical analyses

Statistical techniques to be used for analyzing data generated by this cohort at follow-ups will be described at a future date. Data reported here were analyzed using the statistical package for the social sciences (SPSS Inc., Chicago, IL) and R version 2.8.1 (RDevelopmentCoreTeam, 2005). Statistical measures included analyses of variance (ANOVA), Kruskal-Wallis tests and other non-parametric statistical tests, employed according to the characteristics of specific data elements, the normality or otherwise of their distribution and their suitability for comparison by statistical means. A strength of the AIBL study is its collaboration with the large and respected mathematical and statistical division of CSIRO for future data analyses.

Results

This section gives an overview of our initial results across a range of measures and indicators, but it should be noted that much more detail will be included in subsequent, more specialized publications, which will focus on specific aspects of this cohort.

Composition of the AIBL cohort

Figure 1 shows the total numbers of volunteers screened and assessed, the initial category to which each volunteer or referred participant was assigned prior to assessment, and the final category of allocation after assessment and clinical review.

In all, 1166 individuals presented for AIBL assessment. Fifty-four individuals were excluded, resulting in a baseline cohort of 1112 participants. These included 211 with NINCDS-ADRDA AD (180 probable and 31 possible) and 133 who met Winblad criteria for MCI (77 amnesic multi-domain, 49 amnesic single-domain, 6 non-amnesic multi-domain, 1 non-amnesic single-domain). There were 768 “healthy control” (HC) participants, of whom 396 complained about their memory and 372 did not. Thirty-nine HC individuals (3.5%) both reported and manifested consistent slight forgetfulness or partial recollection of events on testing and yet did not fulfill criteria for MCI or dementia; these individuals were classed as healthy controls with a CDR of 0.5.

Of the 54 individuals (11 putative AD participants, 18 presenting as diagnosed MCI patients and 25 reporting to be healthy controls) who presented for assessment but were unsuitable for inclusion in the cohort, the most common reasons for exclusion were excessive alcohol consumption, past serious head injury, current clinical depression, withdrawal of consent and history of stroke(s). Specifically, volunteers were excluded as follows: 16 volunteers had a history of stroke(s), 6 had history of past serious head injury, 6 had excessive alcohol intake, 2 had epilepsy, 2 had an existing diagnosis of frontotemporal dementia, 2 had Parkinson’s disease, 2 were taking morphine at the time of assessment, 1 had a previous episode of amnesia, 1 had previously been admitted to hospital for hypoxia, 1 had insufficient English to complete the assessment, 1 had depression not apparent at screening, 5 volunteers did not have enough information gathered at assessment (e.g. due to advanced dementia), and 9 withdrew consent.

Within the inception cohort, 31 of the AD participants were classified as having possible (rather than probable) AD according to NINCDS-ADRDA criteria, due to the following reasons: 15 had a history or neuroimaging evidence of asymptomatic minor stroke, TIA or recovered head injury; 4 had current atrial fibrillation and/or history of aortic aneurysm; 1 had Parkinsonian symptoms and recently treated depression; 1 had a previous (now revised) diagnosis of progressive aphasia; 1 had epilepsy; 6 had abnormal blood

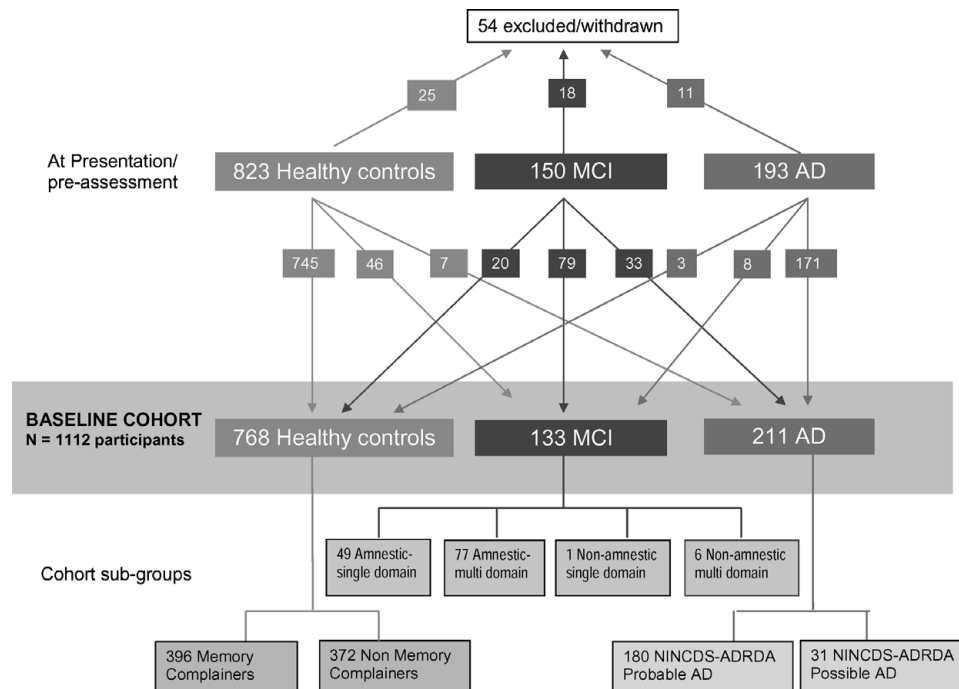


Figure 1. Composition of the AIBL cohort: screening, assessment and cohort sub-groups.

pathology results (i.e. anemia, low folate, etc.); 1 reported previous excessive alcohol intake many years prior to the development of AD; and 2 had atypical clinical presentations of AD. For those AD participants who reported excessive alcohol intake, history of head injury, or past depression, the clinical panel reviewed the cases in detail to ensure that the dementing process occurred after, and in isolation from, the possible confounding history. For each of these 31 cases, the clinical review panel determined that the dementia had clinical AD features and that the potentially confounding diagnosis or history did not appear to account for the progressive dementing illness exhibited by the study participants.

Following detailed review by the clinical panel, a small proportion of AD and MCI cases did not meet the relevant diagnostic criteria (NINCDS-ADRDA criteria for probable or possible AD, or Winblad criteria for MCI), and therefore were reallocated to a different category. Specifically, eight putative AD participants did not have significant impairment of social or occupational functioning, and instead fulfilled Winblad criteria for MCI. Three apparent AD cases were reclassified as healthy control participants; two of these people had been diagnosed with AD by clinicians relatively inexperienced in the diagnosis and management of dementia, and one had been incorrectly classified at presentation.

Consistent with previous research (Larrieu *et al.*, 2002; Solfrizzi *et al.*, 2004; Kryscio *et al.*, 2006), MCI proved to be the most mutable diagnosis. Thirty-three participants presenting with a diagnosis of MCI previously made by a clinician now had significant impairment of social or occupational functioning confirmed by informant history, and a neuropsychological profile consistent with AD, and therefore were reallocated to the AD category. Twenty participants with an MCI diagnosis made by the referral source did not demonstrate cognitive functioning at least 1.5 SD below age-adjusted norms on any cognitive tests, and were thus reallocated at baseline to the healthy control group.

Seven participants who volunteered to take part as healthy controls were found on testing to have both cognitive deficits and an informant history indicating significant impairment of social or occupational functioning that met DSM-IV and NINCDS-ADRDA criteria for AD. Forty-six participants who volunteered to take part as healthy controls scored 1.5 SD below the age-adjusted mean on at least two cognitive assessment measures, and either personally, or through an informant, reported subjective memory difficulties, but had substantially intact social and occupational functioning. These 46 individuals were reallocated to the MCI group.

Table 1. Baseline confirmed classification and demographic characteristics for each group

	HC	MCI	AD
N	768	133	211
Mean age (SD) (years)	70.0 (7.0)	75.7 (7.6)	78.0 (8.6)
Gender (%male/ female)	43 / 57	44 / 56	38 / 62
Mean MMSE (SD)	28.9 (1.2)	26.2 (2.6)	19.0 (5.2)
CDR			
Mean sum of boxes (SD)	0.03 (0.15)	1.23 (0.82)	5.72 (2.91)
Mean overall score (SD)	0.03 (0.12)	0.50 (0.00)	1.00 (0.53)
ApoE ϵ 4 carriers (%)	27	51	63

HC = healthy controls

MCI = participants with Mild Cognitive Impairment

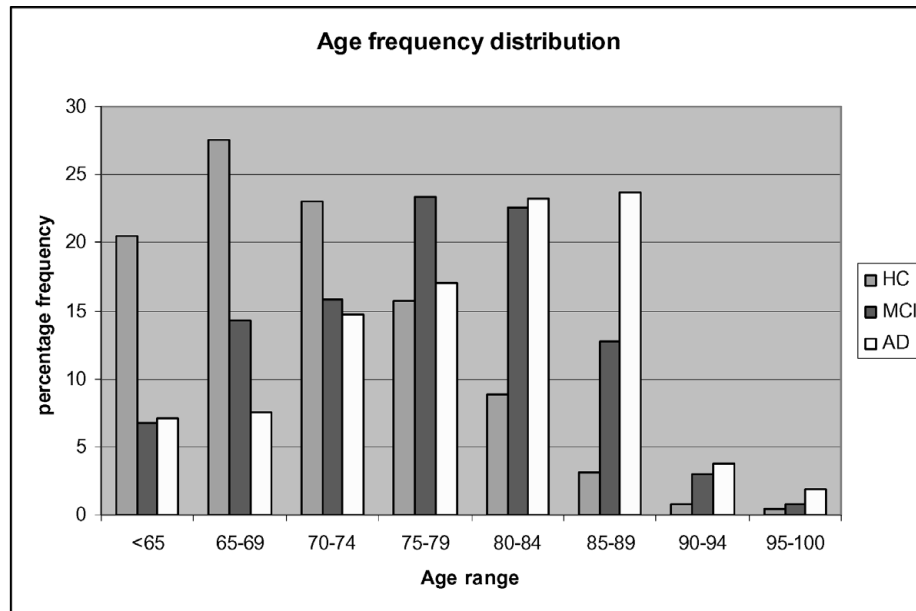
AD = participants with Alzheimer's disease

Table 1 presents information about the 1112 individuals who formed the baseline AIBL cohort. There was a greater percentage of females than males in each group (HC = 57%, MCI = 56%, AD = 62%). The AD participants had MMSE scores ranging from 0 to 28 (median 20) and CDR ratings consistent with "questionable" (CDR = 0.5; 68 AD participants), mild (CDR = 1; 114 AD), moderate (CDR = 2; 25 AD) or severe (CDR = 3; 4 AD) dementia. All MCI participants had a CDR of 0.5 and their MMSE scores ranged from 17 to 30 (median 26). Only two MCI volunteers had a MMSE of less than 20, and these cases were thoroughly reviewed by the clinical review panel. The consensus decision for these cases was that there were no significant difficulties with activities of daily living. Both of these subjects had received only limited schooling. The MMSE scores of healthy controls ranged from 24 to 30 (median 29), and all but 39 had a CDR of 0.

Figure 2 shows the age distribution of the cohort. The healthy control participants were significantly younger than the MCI and AD participants ($p < 0.01$). However the HC group was much larger than the MCI and AD groups combined and contained a substantial number of very elderly healthy participants, which is sufficient to compare AD and MCI participants with aged-matched controls if and when necessary.

Demography

The majority of participants in the cohort were either married (70% of HC, 57% of MCI, 60% of AD) or widowed (11% of HC, 21% of MCI, 24% of AD), and most participants primarily spoke English at home (98% of HC, 92% of MCI, 91% of AD). Those who spoke a language other than English at



HC = healthy controls
MCI = participants with Mild Cognitive Impairment
AD = participants with Alzheimer's disease

Figure 2. Age distribution for each group.

home were nevertheless fluent in English, as lack of fluency in English was an exclusion criterion. Involvement in organized community activities, such as membership of Probus or senior citizen clubs, Returned Servicemen's League clubs and/or sporting clubs was highest in the HC and MCI groups, as was expected (68% of HC, 67% of MCI); however, nearly half (47%) of AD patients remained involved in community organizations at some level. Approximately one third of the cohort reported having at least one pet (33% HC, 28% of MCI, 33% AD). The cohort was well educated, with 47% of HC, 58% of MCI and 42% of AD participants reporting 13 or more years of education. Results of the Wechsler Test of Adult Reading (WTAR) revealed estimated mean premorbid IQ scores of 101 for AD patients, 105 for MCI participants and 108 for HCs, with significant differences between each of the groups (HCs demonstrated significantly higher mean IQ than MCIs, with ADs scoring significantly lower than MCIs). The majority of participants were right handed (88% of HC, 86% of MCI, 87% of AD), in line with the world population proportion of right-handedness (Corballis, 2009).

Neuropsychology

Table 2 presents the mean and standard deviation of normed and age-adjusted measures for the neuropsychological tasks, and the results of between-groups one-way analysis of variance (ANOVA) for each measure. These groups

differed significantly on all measures ($p < 0.01$). Furthermore, planned comparisons demonstrated that the HC group performed significantly better than MCI participants, and MCI participants significantly out-performed those with AD on all measures (all $p < 0.01$).

Table 3 presents the mean and standard deviation of all measures of the CogState battery, and the results of the Kruskal-Wallis significance test for each measure. These findings demonstrate significant differences between the three groups on all measures ($p < 0.05$). Further, Wilcoxon ranked-sums tests showed that HC participants performed significantly better than the MCI participants on all measures of the CogState battery ($p < 0.0001$). The MCI participants performed significantly better than the AD participants on the One Card Learning task and the Continuous Paired Associate Learning Task ($p < 0.05$). There were no other significant differences between the MCI and AD participants.

Overall, these cognitive findings were highly consistent with those expected in participants classified as HC, MCI and AD and support the accuracy of participant assignment in this cohort.

Baseline medical characteristics and medication use

Table 4 presents vital signs (heart rate, blood pressure, weight, height and abdominal circumference and body mass index) for the three groups. The only difference between groups was observed in

Table 2. Baseline cognitive performance measures for each group

	HC M (SD)	MCI M (SD)	AD M (SD)	ANOVA	
				F	P
CVLT-II					
T-score learning (1–5)	60.63 (10.93)	37.89 (9.74)	26.28 (9.41)	899.94	<0.001
Short delay free recall Z-score	0.87 (1.01)	–1.39 (0.97)	–2.22 (0.66)	930.86	<0.001
Long delay free recall Z-score	0.80 (0.98)	–1.64 (0.99)	–2.55 (0.64)	1128.80	<0.001
Recognition: true positives Z-score	0.10 (0.83)	–1.20 (1.47)	–1.92 (1.92)	247.48	<0.001
Recognition: false positives Z-score	–0.21 (0.92)	1.18 (1.39)	2.12 (1.87)	304.14	<0.001
Recognition d'	0.47 (0.96)	–1.23 (1.02)	–2.04 (1.21)	513.57	<0.001
LOGICAL MEMORY					
Recall 1 raw score	12.93 (3.88)	6.42 (3.67)	3.13 (2.80)	623.95	<0.001
Recall 2 raw score	11.44 (4.02)	3.83 (3.75)	0.95 (1.98)	720.38	<0.001
Pass/Fail*	91/9%	31/69%	19/81%	713.96	<0.001
RCFT					
Copy Z-score	–0.49 (1.07)	–1.48 (2.06)	–3.16 (3.49)	157.29	<0.001
Short Recall Z-score	0.50 (1.34)	–0.81 (1.22)	–1.91 (0.98)	273.37	<0.001
Long Recall Z-score	0.54 (1.45)	–1.02 (1.49)	–2.14 (1.03)	279.39	<0.001
Recognition Z-score	0.32 (1.30)	–1.19 (1.73)	–2.94 (2.33)	294.27	<0.001
DIGIT SPAN					
Scaled score	12.03 (2.86)	11.06 (2.71)	9.07 (2.97)	83.93	<0.001
DIGIT SYMBOL CODING					
Scaled score	11.70 (2.59)	9.67 (2.88)	6.63 (2.95)	236.07	<0.001
D-KEFS verbal fluency					
FAS total Z-score	12.05 (3.45)	9.96 (3.80)	7.31 (3.81)	139.75	<0.001
Category total Z-score	12.40 (3.06)	8.92 (3.46)	5.25 (2.85)	424.34	<0.001
Fruit/Furniture total Z-score	12.16 (3.22)	8.15 (3.58)	4.55 (3.12)	417.88	<0.001
Fruit/Furniture Switching Z-score	12.18 (2.97)	8.50 (3.44)	5.05 (3.17)	411.18	<0.001
BNT					
AU No cue Z-score	0.75 (0.62)	0.18 (1.14)	–1.15 (1.94)	225.23	<0.001
CLOCK raw score	9.76 (0.72)	9.29 (1.26)	7.22 (2.38)	318.07	<0.001
WTAR estimated IQ	111.60 (6.59)	108.80 (8.87)	104.3 (12.37)	57.98	<0.001
STROOP					
Dots Z-score	–0.04 (1.20)	0.58 (1.92)	2.07 (4.84)	58.00	<0.001
Words Z-score	0.07 (1.15)	1.06 (2.12)	4.62 (10.74)	71.16	<0.001
Colors Z-score	–0.33 (0.95)	0.41 (1.63)	1.83 (3.68)	97.82	<0.001
C/D Z-score	–0.31 (0.83)	0.08 (1.04)	0.59 (1.72)	46.38	<0.001

*Based on education corrected cut-off scores for delayed recall of the first paragraph of the WMS Logical Memory subtest, as defined by the Alzheimer's Disease Neuroimaging Initiative (ADNI).

CVLT-II = California Verbal Learning Test (second edition).

RCFT = Rey Complex Figure Test.

D-KEFS = Delis-Kaplan Executive Function System.

BNT = Boston Naming Test.

WTAR = Wechsler Test of Adult Reading (based on U.S. norms).

HC = healthy controls; MCI = participants with Mild Cognitive Impairment; AD = participants with Alzheimer's disease.

the weight measures ($p < 0.05$), with AD patients weighing less than both HCs and MCIs. However, this difference was mediated by age, with older volunteers observed to weigh less than younger volunteers ($p < 0.05$).

With regard to family history of dementia, 28% of AD participants reported that they had a first degree relative with dementia. The mother was the most common family member reported to have had dementia (33 of 58; 57%). Of those

AD participants who reported a family history, 11 (19%) reported multiple first degree family members to have had dementia. In the MCI group, 37% (49 participants) reported that they had a first degree relative with dementia. Again, the most common family member to have had dementia was the participant's mother (32; 65%). Of the MCI participants who reported a family history, three (6%) reported multiple first degree family members to have had dementia. Family history of dementia in

Table 3. Baseline CogState scores for each group – mean (SD)

TASK	HC	MCI	AD	KRUSKAL P WALLIS H	
Detection task reaction time (log10 transformed)	2.52 (0.12)	2.56 (0.14)	2.55 (0.09)	8.68	<0.05
Identification task reaction time (log10 transformed)	2.71 (0.07)	2.76 (0.09)	2.77 (0.1)	22	<0.0001
One Card Learning Task accuracy (arcsine transformed)	1.02 (0.11)	0.93 (0.11)	0.85 (0.1)	42.29	<0.0001
One-Back Task accuracy (arcsine transformed)	1.33 (0.15)	1.21 (0.16)	1.13 (0.14)	32.4	<0.0001
One-Back task reaction time (log10 transformed)	2.93 (0.09)	3.02 (0.08)	3.03 (0.11)	39	<0.0001
CPAL (errors)	39.07 (26.33)	61.77 (26.18)	82.33 (32.26)	58.38	<0.0001

HC = healthy controls

MCI = participants with Mild Cognitive Impairment

AD = participants with Alzheimer's disease

Table 4. Mean (SD) vital sign measures for each group

	HC	MCI	AD
Height (cm)	166.6 (11.2)	165.5 (8.7)	164.8 (9.5)
Weight (kg)	74.2 (15.0)	70.2 (12.4)	66.7 (13.3)
Blood pressure systolic (mm Hg)	137.9 (15.4)	141.0 (14.6)	138.1 (15.6)
Blood pressure diastolic (mm Hg)	78.6 (9.7)	79.1 (10.2)	80.0 (11.1)
Heart rate (bpm)	67.1 (10.1)	67.4 (9.3)	68.0 (10.1)
Abdominal circumference (cm)	91.4 (15.2)	90.8 (12.4)	91.7 (12.0)
Body Mass Index (BMI)	27.4 (18.9)	25.6 (3.9)	24.8 (4.4)

HC = healthy controls

MCI = participants with Mild Cognitive Impairment

AD = participants with Alzheimer's disease

the HC group was also common. Three-hundred-and-twenty-eight (43%) HC participants reported that they had a first degree relative with dementia; 175 (53%) were memory complainers, 153 (47%) were not memory complainers. Forty-two (13%) HC participants reported that they had multiple first degree relatives with dementia. As with the AD and MCI participants, the most common family member reported by the HC participants to have had dementia was their mother (228; 70%).

Table 5 presents self-reported current and past medical history. Participants from all three groups had a range of comorbid medical conditions, including current or past history of hypertension (297 HC, 52 MCI, 48 AD), diabetes mellitus (53 HC, 14 MCI, 23 AD), treated thyroid disease (82 HC, 11 MCI, 16 AD) and gastrointestinal system complaints (250 HC, 35 MCI, 44 AD).

Prescription and “over the counter” medication

Most participants, regardless of classification, reported taking medications. Overall, 79% of HC, 87% of MCI and 97% of AD participants were taking at least one prescription or over the counter medication. The proportion of participants taking medications was significantly greater in the AD group than the MCI group, with the HC

group having the significantly lowest proportion of participants taking medications.

Participants took between 0 and 13 medications per day (average intake: HC = 2.4 + 2.2, MCI = 3.2 + 2.6, AD = 3.8 + 1.2), and again there were significant differences between the groups, with AD participants taking more medications daily than MCI participants, and HCs taking the least number of medications.

Consistent with the high levels of cholesterol in this age-group, the most commonly prescribed medication for all participants was the cholesterol-lowering agent atorvastatin calcium (107 HC, 19 MCI, 30 AD). Occasional paracetamol and/or aspirin were also within the top ten medications listed by all three groups (166 HC, 38 MCI, 63 AD).

Of the 211 confirmed AD participants, 134 (64%) were prescribed AD medication at the time of assessment. The most common AD medication was donepezil (74 AD patients), followed by galantamine (43 patients), and rivastigmine (5 patients). An additional six patients were taking a combined donepezil/memantine treatment, and six were taking combined galantamine/memantine treatment.

Although there were 77 AD volunteers who were not taking AD medications at baseline, it should be noted that this group includes 33 participants who presented as MCI and six participants who presented as HC (and were subsequently

Table 5. Percentage of participants in each group who reported current or past history of specific medical conditions

	HC	MCI	AD
Hypertension	38.9	39.1	37.4
Myocardial infarction	4.6	5.3	6.2
Diabetes mellitus	6.9	10.5	10.9
Visual Color Deficit	3.4	1.5	2.8
Cancer*	17.1	15.0	15.2
History of falls	11.1	25.6	22.7
Thyroid disease	10.7	8.3	7.6
Gastrointestinal disorders	32.6	26.3	20.9
Arthritis	51.4	48.1	42.7
Joint replacement	10.7	12.8	9.5
Liver disease including hepatitis	4.4	5.3	1.9
Kidney disease	7.7	9.0	3.8
Depression	15.4	23.3	27.0
Anxiety	15.0	23.3	23.2
Other psychiatric disorders	1.3	3.8	3.8

*Most were skin cancers. Those that were not (e.g. bowel cancer) had been cured or had been in remission for more than 2 years.

#Most often gastro-esophageal reflux or diverticular disease.
 HC = healthy controls; MCI = participants with Mild Cognitive Impairment; AD = participants with Alzheimer's disease.

reallocated to the confirmed AD group after clinical panel review). Of the 33 volunteers who presented as MCI and were subsequently classified as AD, four were taking donepezil and nine were taking galantamine at the time of assessment. In addition, several of the AD participants who presented as AD and who were not on AD therapy had been recently diagnosed and had not yet started their treatment.

One subject who presented having been diagnosed with AD by a practitioner inexperienced in its diagnosis and management was taking donepezil, despite the clinical review panel observing no evidence of impairment in either their past or current social and occupational functioning, or in their cognitive profile, and this participant was reallocated to the HC group. Finally, one AD patient who was misclassified as HC at presentation was taking donepezil.

The AD group had a significantly higher proportion of antidepressant use (6% HC, 15% MCI, 25% AD). The reported intake of benzodiazepines was low in all groups (2% HC, 6% MCI and 6% AD), with most using them on an "as required" basis.

Nutraceuticals

A large proportion of the cohort was taking nutraceuticals (i.e. vitamins, minerals, herbs and other supplements). The number of nutraceuticals taken daily ranged from 0 to 13 (HC = 1.7 + 2.0, MCI = 1.3 + 1.8, AD = 1.1 + 1.6), and the proportion of HCs taking nutraceuticals was significantly

Table 6. Baseline anxiety and depression scores on the HADS and GDS measures for each group.

	HC M (SD)	MCI M (SD)	AD M (SD)	ANOVA	
				F	P
HADS					
A	4.4 (2.9)	4.9 (2.9)	4.9 (3.9)	4.29	<0.001
D	2.6 (2.3)	3.7 (2.6)	4.0 (3.7)	28.52	<0.001
GDS					
	2.0 (1.4)	2.0 (1.8)	2.9 (2.2)	91.11	<0.001

HADS scores can range from 0 – 18. GDS scores can range from 0 – 15.

HADS = Hospital Anxiety and Depression Scale (A = anxiety subscale score, D = depression subscale score).

GDS = Geriatric Depression Scale.

HC = healthy controls; MCI = participants with Mild Cognitive Impairment; AD = participants with Alzheimer's disease.

higher than in the AD group. Vitamin supplements were the most commonly reported item taken by all participants, with over half the cohort (HC = 60%, MCI = 52%, AD = 53%) taking a vitamin supplement.

Symptoms of depression and anxiety

Table 6 shows GDS and HADS measures for the three groups. While the mean scores for each group were low (suggesting low levels of anxiety and depression) due to exclusion of high GDS scorers in the HC group at screening, analysis of variance demonstrated that MCI and AD participants tended to have significantly more symptoms of anxiety and depression than HC participants (all $p < 0.05$).

Forty (5.3%) HC participants scored within the clinically significant range on the anxiety subscale of the HADS (i.e. $\geq 10/18$) and a further 121 (15.9%) had scores within the probably clinically significant range (i.e. 7–9). Ten (1.3%) HC participants scored within the clinically significant range on the depression subscale (i.e. $\geq 10/18$) and a further 37 (4.9%) had scores within the probably clinically significant range (i.e. 7–9).

Consistent with many previous research publications (Jost and Grossberg, 1996; Mega *et al.*, 1996; Lyketsos *et al.*, 2002; Rozzini *et al.*, 2008), current and past history of depression and anxiety rates were higher in the AD and MCI groups, compared to HCs (15% of HC, 23% of MCI and 27% of AD participants reported current or past depression; 14% of HC, 23% of MCI and 23% of AD participants reported current or past history of anxiety).

Blood samples

A summary of ApoE genotyping results is presented in Table 1. As expected, the number of ApoE $\epsilon 4$ carriers was highest in the AD

group (HC = 27%, MCI = 51%, AD = 63%), with significant differences between the groups.

PiB imaging

Two-hundred-and-eighty-seven participants (53 AD, 57 MCI, 177 HC) had a 11C-PiB-PET scan, as previously described (Pike *et al.*, 2007) and a 3D T1-weighted MPRAGE, T2 FSE, and FLAIR sequence MRI for screening and co-registration with the PET images.

Health and lifestyle

A total of 100 AIBL participants (16 AD, 20 MCI and 64 HC) underwent DEXA scans. In addition, 91 participants participated in the ActiGraph monitoring component (6 AD, 8 MCI and 77 HC). There were 31 participants who completed both DEXA and ActiGraph components (2 AD, 1 MCI and 29 HC).

Discussion

The AIBL study has assembled a large cohort of individuals who can be assessed, compared and then followed over a long period of time in order to facilitate prospective research into AD. This is the largest cohort study of its kind in Australia (and one of the largest worldwide) to have thoroughly assessed individuals with and without AD, and with varying levels of risk for developing AD. The participants represent a group of highly motivated and well-characterized individuals whose cognitive data, blood samples, imaging results, and lifestyle information will be examined longitudinally at regular intervals.

Classifications of AD and MCI within the cohort were made according to established, internationally recognized criteria after thorough review by a multi-disciplinary group of academic clinicians experienced in the assessment, diagnosis and management of late-life cognitive disorders, particularly AD and MCI. Most participants who presented with diagnoses of AD from their treating clinician had these diagnoses confirmed by the clinical review panel, demonstrating the relatively robust nature of this clinical diagnosis and the expertise of the referring clinicians. In contrast, MCI cases were by far the most difficult group to characterize. A significant percentage of those who presented with an MCI diagnosis from their treating clinician proved not to fulfill internationally-agreed MCI criteria (Winblad *et al.*, 2004). However, it is possible that the referring clinicians were using different diagnostic criteria from Winblad and colleagues, as these have changed with time and are

evolving more rapidly than AD diagnostic criteria. Also, it is known that some individuals classified as having MCI will progress to exhibiting clear symptoms of AD within months, while some others will show cognitive improvement over time (Petersen *et al.*, 1999). The reliability of the current MCI diagnostic classifications needs to be tested over time. The AIBL cohort represents an opportunity to examine the biological, imaging or lifestyle markers which may be of use in clinical classification. Using the standard criteria (as employed in this study), we would expect to see progression to AD from MCI in 10–20% of this group annually, with approximately one-third of MCI cases never progressing to AD. Both the rate of ApoE ϵ 4 allele frequency in the MCI group compared to our AD and HC groups, and the neuropsychological testing results of the MCI group, suggest that we have identified a group of individuals whose characteristics are, in many respects, intermediate between HC and AD participants.

In this study the term HC referred predominantly to the absence of cognitive difficulties. As expected in a group of over 700 individuals aged between 60 and 96, most were affected by one or more chronic but controlled medical conditions, and a past history of some degree of depression or anxiety was common. Our HC participants were taking a range of medications and had medical histories which indicated the presence of a range of medical conditions typical of this age group. Where HC participants had evidence of illnesses or medication use that could have affected cognitive function, their cases were reviewed in detail. For example, we were careful to ensure that individuals with a history of hypothyroidism were taking thyroxine and had normal TSH levels. Most antidepressants taken were types that do not usually affect cognition. For the small proportion of individuals who were taking benzodiazepines, dosage was typically low, often taken only occasionally, and cognition was nevertheless within normal limits on testing. HC participants who were assessed as performing poorly on cognitive tests due to current medical illness, medical history or medication use were excluded from the cohort as noted in the study methodology. It would have been possible to exclude all HC individuals who had recovered from previous depression, or were affected by hypertension (or any other illness associated with an increased risk of current cognitive impairment or future decline), or to have denied participation to all who took any psychotropic drugs. However, this would have resulted in the selection of a “super-normal” cohort of individuals chosen for extreme health, whose parameters would not have been

comparable with those of our AD and MCI groups. The characteristics of the current cohort of HCs therefore allow for a better comparison between groups based on their similar medical histories.

The term HC may be a misnomer when applied to this large group of individuals with a range of risk factor profiles for AD. This point notwithstanding, the neuropsychology results obtained from our HC participants give an excellent baseline against which to detect even subtle future changes. Tracking change in this group over time should provide valuable information regarding the profiles (biological, psychological, medical, social and genetic) of individuals aged over 60 who are most likely to develop AD, in addition to offering an important insight into rates of change in cognition and other measures over time in healthy elderly people. Of specific interest will be the differences (if any) seen between those HCs who are “subjective memory complainers” and those HCs who do not report memory concerns. To date there is conflicting evidence as to whether subjective memory impairment is associated with an increased risk for developing cognitive impairment (for a review, see Jonker *et al.*, 2000). Fifty-two percent of the HCs in this cohort were subjective memory complainers, which is in line with prevalence of memory complaint assessed in other community-based studies, with rates ranging from a quarter to over a half of healthy volunteers (Jonker *et al.*, 2000).

It should be noted that this cohort was recruited through advertisements seeking volunteers for a study into memory and aging, and there is likely to have been some inherent self-selection bias towards those with a family history of dementia who might be expected to exhibit more interest in such research than individuals with no exposure to dementia in their family members. However, proportions of ApoE $\epsilon 4$ carriers in this cohort were consistent with previous estimates of the Australian population (Corbo and Scacchi, 1999; Martins *et al.*, 1995) and do not suggest a significant over-selection of $\epsilon 4$ carriers.

Subsequent detailed analysis of the baseline cross-sectional data presented here will provide valuable information on links between cognition, brain amyloid burden, structural brain changes, biomarkers, and lifestyle. The future research yield from the AIBL cohort should add much to our knowledge about AD. Currently, 18-month follow-up assessments are taking place, and, in addition to repeating baseline assessments participants are being asked to give consent to future *post mortem* brain donation and autopsy so that plaque and tangle counts as well as total brain amyloid burden can be determined in due course for at least one quarter of the cohort. The existence of a

well-established Australian brain donation network will facilitate this goal. At 18-month follow-up at least 100 participants will donate CSF obtained at lumbar puncture to permit determination of A β /tau ratios in CSF and to cross-validate PiB PET findings and A β blood amyloid levels. Dependent on continued funding, all consenting members of this cohort will be followed at 18-month intervals until death, with the primary aim of determining which baseline characteristics are predictive of future cognitive decline. The cluster collaboration demonstrates the increased capacity for recruitment with multicenter collaboration necessary to achieve large sample size with in-depth clinical examination. In addition, the cluster strategy with specialized researchers within broad themes allows the benefit of a combination of skills from clinical expertise to basic science and bioinformatics.

The AIBL dataset is a unique Australian resource with international significance, which will assist development of important and robust techniques for early detection of AD, identify lifestyle targets which may delay onset of AD, and provide a valuable cohort suitable for further study of AD.

Conflict of interest declaration

David Ames is the editor and Nicola Lautenschlager is a deputy editor of *International Psychogeriatrics*. This paper was therefore reviewed at arm's length through the office of deputy-editor Professor John O'Brien.

David Darby and Paul Maruff are shareholders in CogState Ltd. and are paid employees of that company.

Description of authors' roles

Kathryn Ellis helped plan the study, coordinated the study, chaired the clinical and cognitive stream, assisted with design and implementation of assessment procedures, served on the study management committee and the clinical panel, and helped to write the paper. Ashley Bush, Colin Masters, Peter Hudson and Ralph Martins helped plan the study and co-led the biomarkers stream. All four had input into the writing of the paper. Ralph Martins led the Western Australia component of the study. CM, PH and RM served on the study management committee. David Darby, Michael Woodward and Nicola Lautenschlager helped to plan the study, participated in clinical panel meetings and referred AD and MCI participants to the study. DD and NL helped plan the clinical and cognitive stream, while MW referred more subjects to the study than any other clinician. All three reviewed drafts

of the paper. Daniela De Fazio participated in the clinical review panel, assessed many of the participants, assisted with data management and reviewed drafts of the paper. Jonathan Foster, Paul Maruff and Greg Savage co-led the clinical and cognitive stream, and (with KE) helped plan the study, devised the neuropsychological test battery (with KE, KP, NL and DD) and reviewed drafts of the paper. Andrew Milner served on the AIBL management committee and worked on drafts of the paper. Kerry Pike helped plan the clinical and cognitive stream, participated in the clinical review panel, helped coordinate the Melbourne neuroimaging site, assessed participants at Austin Health, and reviewed drafts of the paper. Christopher Rowe and Nat Lenzo led the neuroimaging stream. CR serves on the study management committee and helped plan the study. Both reviewed drafts of the paper. Cassandra Szoek is CSIRO theme leader responsible for the AIBL study and worked on drafts of the paper. She is the CSIRO representative on the study management committee. Kevin Taddei helped design the blood protocols, coordinated procedures in Perth and reviewed drafts of the paper. Victor Villemagne coordinated the neuroimaging stream, analyzed all PiB images and reviewed drafts of the paper. David Ames helped to plan the study, led the study, chaired the management group and clinical review panel, referred many of the AD and MCI participants and helped write the paper. The AIBL research group was responsible for the collection and interpretation of the data.

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Appendix 2 – AIBL research partner organizations

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 Neurosciences Australia Ltd (NSA)*
 Edith Cowan University (ECU)*
 Mental Health Research Institute (MHRI)*
 Alzheimer's Australia (AA)
 National Ageing Research Institute (NARI)
 Austin Health
 University of WA (UWA)
 CogState Ltd.
 Macquarie University
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 Sir Charles Gairdner Hospital

*denotes signatories to AIBL legal agreement

DRAFT – NOT FOR GENERAL CIRCULATION UNTIL ACCEPTED FOR PUBLICATION

***Research and Standardization in Alzheimer’s Trials: Reaching
International Consensus***

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KEYWORDS: Alzheimer's disease, diagnosis, early detection, biomarkers, clinical outcomes, cerebral spinal fluid, amyloid imaging, magnetic resonance imaging

ABSTRACT

Alzheimer's disease (AD) is an epidemic facing the entire world. Increased knowledge gained over the past 25 years indicates that AD falls along a clinical and neuropathological spectrum represented as a continuum that extends from preclinical disease in which there are no symptoms, through early symptomatic phases, and finally to AD dementia. The Alzheimer's research community recognizes that imaging, body fluid and cognitive biomarkers contribute to enhanced diagnostic confidence for AD. There has also been emerging consensus regarding the use of AD biomarkers in clinical trials. The use of biomarkers in clinical trials and practice is hampered by the lack of standardization. In response to the emerging need for standardization, an international meeting of AD researchers was held in Melbourne, Australia in March 2012 to bring together key researchers, clinicians, industry, and regulatory stakeholders with the aim of generating consensus on standardization and validation of cognitive, imaging and fluid biomarkers, as well as lifestyle parameters used in research centers worldwide.

1.0 Introduction

Alzheimer's disease (AD) is a core health issue facing the entire world. Increased knowledge gained over the past 25 years indicates that AD falls along a clinical and neuropathological spectrum, which is reflected in the new criteria proposed by both an international working group (IWG) [1] and three workgroups established by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [2-4]. The AD continuum represented in the new criteria extends from preclinical disease in which there are no symptoms, through early symptomatic phases, and finally to AD dementia. The revised criteria also operationalize functional independence more extensively than previous criteria and thus have compromised the categorical distinction between MCI and milder stages of AD dementia [5].

Both the NIA/AA and IWG criteria recognize that biomarkers give enhanced diagnostic confidence for AD. These include molecular biomarkers, in particular low levels of cerebrospinal fluid (CSF) amyloid β 1-42 ($A\beta_{42}$) and elevated levels of CSF total tau and phospho-tau; and imaging biomarkers including amyloid imaging with positron emission tomography (PET), reduced temporoparietal metabolism assessed using fluorodeoxyglucose (FDG)-PET, and whole brain and/or regional atrophy assessed with magnetic resonance imaging (MRI).

There has also been emerging consensus regarding the use of AD biomarkers in clinical trials, particularly for subject selection and assessment of target engagement and biological change [6]. Biomarkers are an integral component of the Dominantly Inherited Alzheimer's Network (DIAN) [7] and Alzheimer's Prevention Initiative (API) [8] studies, which enroll individuals at

high risk of developing AD because of their genetic background, as well as many recent clinical trials. However, the use of biomarkers in clinical trials is hampered by the lack of standardization and by the fact that nearly all biomarker research has been done in specialized research centers using in-house developed methods that have not been well validated in other sites and where enrolled populations are known to differ markedly from the general population. In addition, there are unintended consequences related to greater use of biomarkers, including increased costs and the early identification of individuals when there is little known about prognosis and treatment. Further, there remain many questions about the specificity of various biomarkers. For example, people with non-AD forms of dementia may also have CSF AD biomarker profiles, and many people who are clinically normal have positive CSF or imaging biomarkers. The extent and time-course by which amyloid biomarkers, assessed either in CSF or by PET imaging, predict the cognitive and functional trajectory of a patient remain to be established. Harmonization and standardization in clinical assessment is also needed to enable efficient and informative clinical trials.

The extent to which biomarkers reflect pathological changes that produce symptoms is another area of research that holds great promise but demands standardization. Recent studies, for example, indicate that A β accumulates prior to the onset of clinical symptoms and that by the time symptoms occur, other pathological factors such as neurodegeneration and tau accumulation may be more important [9]. This suggests that therapies targeting amyloid might be more effective if delivered in the preclinical stages of the disease and may explain why some clinical trials of anti-amyloid therapies delivered to symptomatic patients may appear to have failed.

In response to the emerging consensus on the need for standardization, an international meeting of AD researchers was held in Melbourne, Australia in March 2012 to build upon previous work on standardization by bringing together key researchers, clinicians, industry, and regulatory stakeholders with the aim of generating consensus on standardization and validation of cognitive, imaging, and fluid biomarkers, and lifestyle parameters used in research centers worldwide.

2.0 Harmonizing cognitive data in longitudinal trials

Combining data from longitudinal studies conducted over many years and from different populations presents many challenges, but offers tremendous benefits in terms of better understanding of both normal aging and the development of dementia. For example, the Mayo Clinic Study of Aging (MCSA) created a patient registry in 1986 utilizing instruments widely available in the field so as to make their work applicable to practicing physicians. Over time, advances in the field have resulted in changes in these instruments; however, the latent cognitive constructs underlying these tests, such as processing speed, are fairly constant over time allowing the data to be combined, albeit with some non-trivial statistical modeling.

While utilization of the same tests over and across studies makes it easier to pool data, there are also concerns that the most widely used tests, such as the Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog), lack sensitivity to detect cognitive change in high-functioning individuals and in the earliest stages of the disease. In the Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing (AIBL, www.aibl.csiro.au), for example, participants tend to be functioning at a higher level than the general population, with high levels of education and cognitive reserve that make it difficult to detect mild levels of cognitive impairment when

comparing to normative datasets. Using a simple test such as the Wechsler Test of Adult Reading as a measure of estimated IQ, which is impervious to strategic influence, could help; however, it is a blunt instrument with a low ceiling and does not target individuals with non-verbal strengths. Another strategy is to tap automatic rather than strategic processing, such as reaction time and error rate, and/or to assess intra-individual discrepancies in cognitive measures. However, when using these newer assessment tools, it will be important to correlate them with existing measures.

For diagnostic purposes and clinical trials, assessing change over time is more useful than a single cognitive test with a standardized cutoff. Moreover, cognitive assessment is most valuable when evaluated in the context of other biomarker tests as well as subjective memory complaints (i.e., concerns about memory) obtained by informant interviews. Thus, in terms of cognitive tests, the field does need to develop standards regarding continuous variables and interpretation of findings with consideration of inter-population differences.

3.0 Standardizing biomarker assessments

While neuropathology has long been the gold standard for diagnosing AD, this may be changing as neuroimaging and other biomarkers particularly in CSF, show utility in early diagnosis [10]. However, none of the currently available biomarkers by themselves fully capture the status of disease in an individual and much of what we know about the pathophysiology of the disease is not captured by any biomarker. Moreover, as we learn more about the disease process, new biomarkers are expected to be discovered. Given the impending expansion of this area in Alzheimer's research, the need for standardization is essential to augment progress from bench to bedside.

3.1 Structural MRI

Neuroimaging illuminates anatomical characteristics of AD, yet there is still much to learn about the relationship between anatomy and behavior. Structural magnetic resonance imaging (MRI), which documents regional brain atrophy and synaptic loss, particularly in the hippocampus, caudate nucleus, and medial temporal lobe, has been widely used in research and has been clinically validated, but is not routinely used in clinical practice [6]. Ample literature illustrates the diagnostic effectiveness of MR measures in distinguishing affected persons from aged-matched controls and predicting the progression of the disease; and longitudinal measures show good correlation with concurrent cognitive change. Brain atrophy is also being considered as a surrogate outcome in clinical trials of disease-modifying drugs [11]. In addition, structural MRI is used to exclude other etiologies and to identify the presence of cerebral microhemorrhages, white matter hyperintensities, and lacunar infarcts, which appear as lesions on gradient echo MR sequences, some of which might provide a link between amyloid and vascular causes of dementia [12]. MRI has also been used to detect amyloid related imaging abnormalities (ARIA) in amyloid modifying treatment trials [13].

Structural MR is widely available around the world and has been qualified by the European Medicines Agency (EMA) as a marker of predementia for enriching clinical trials [14].

However, there is as yet no standardized methodology for acquisition or analysis. Since there is tremendous variability introduced at every step in the process – preparation of subjects, use of different models of scanners and different imaging protocols, and variability among technologists, software, and readers – standardization is critical for utilizing these measures in

clinical trials and translating them into clinical practice. The Alzheimer's Disease Neuroimaging Initiative (ADNI) has created generic protocols for acquiring and pre-processing images, and is working with the European Alzheimer's Disease Centers (EADC) to harmonize protocols for automated segmentation and image analysis [15, 16] that would provide more consistent, quantitative results. A Delphi panel of experts has converged on a single protocol that covers 100% of the hippocampus; this protocol next needs to be validated.

3.2 Amyloid imaging

In 2004, Klunk et al. reported the first human study using PET imaging with an amyloid tracer called Pittsburgh compound-B (PiB), which enabled the visualization of amyloid deposits in the brains of individuals with AD [17]. Since that time, amyloid imaging has become an important research tool and is widely used in therapeutic trials to assess reduction in amyloid burden. Now, with the introduction of new radioligands and the recent FDA approval of one of these, florbetapir, amyloid imaging is quickly moving into clinical use.

As with MRI, standardization is essential if PET scans are to be used in clinical trials and in the clinic. In addition to standardizing subject state, imaging protocol (as many as 30 protocols are available), instrumentation (three different systems), processing of data, quantitation, and analysis, PET also requires standardization of the radiopharmaceutical used. ¹¹C-PiB has been most widely studied, but the newer tracers including florbetapir [18], florbetaben [19], flutemetamol [20], and AZD4694 [21] all use F-18 rather than C-11 as the radiolabel and thus have a longer half-life, allowing for wider distribution. All of these radiopharmaceuticals show excellent correlation both with PiB and autopsy amyloid burden data, although the numerical

values, and thus the cutoffs to differentiate normal from AD pathology, differ. These differences in tracer performance characteristics affect sensitivity and specificity, which is the subject of further investigation. Instrument resolution and reconstruction algorithms also affect results, and the reference region used to normalize data has the largest effect on results. Thus, all of these parameters require standardization, particularly as PET imaging becomes more widely used at clinical and research centers that have little familiarity with the technology.

3.3 Functional imaging

PET is also used to assess metabolic activity in specific regions of the brain, which reflects neurodegeneration and loss of synaptic activity. This is accomplished by assessing glucose uptake with FDG-PET, a technique that is widely used across many areas of medicine, and which has been shown capable of differentiating AD from other causes of dementia [22]. For FDG-PET in AD, standardization is required for many of the same parameters as for PET amyloid imaging. ADNI has developed methods to allow pooling of scans from a wide variety of scanners and sites through standardization of the acquisition protocol and specification of the optimal image reconstruction for each make and model of PET and PET/CT scanner. However, to then reduce variability that results from the wide range of camera and reconstruction parameters, the images are smoothed, resulting in loss of resolution and potentially, loss of information and worsening of partial volume and spill-over effects. In addition, no conclusions have been reached on the best method to then analyze the scans. A comparison of three different automated data analysis techniques that produce a single numerical value concluded that all were similar in their ability to classify patients by disease severity [23], although the usefulness of that metric in comparison to other biomarkers has not been established. The most widely distributed quantitative aid to FDG PET analysis is used at over 200 sites worldwide for both research and

clinical application. This technique has been demonstrated to greatly improve the interpretation of clinical scans by less experienced readers [24].

Functional MRI (fMRI) is used to assess the functional integrity of brain networks, including those involved in memory and other cognitive domains, which are affected in early AD [25].

Studies have demonstrated disruptions in resting state functional connectivity in the default mode network of cognitively normal people with amyloid deposition [26] and even in ApoE ϵ 4-positive individuals with no biomarker evidence of amyloid deposition [27], suggesting that these changes occur quite early in the disease process and may be among the earliest detectable signs of disease. While fMRI has been used only sparingly in research to this point, it offers considerable potential for use clinically and in clinical trials if standardization is pursued.

Although the preprocessing and processing of functional connectivity data is quite complex, there are many fMRI software programs available publicly that have shown utility in other disease states. Therefore, standardization is expected to be straightforward.

3.4 CSF biomarkers

The amyloid cascade hypothesis, wherein accumulation of A β drives the neurodegenerative process of AD, has dominated thinking about the pathogenesis of Alzheimer's disease, and has been supported by CSF biomarkers studies which show that the combination of low CSF A β ₄₂, increased CSF total tau (t-tau), and increased phosphorylated tau (phospho-tau) has a high diagnostic accuracy for AD [28]. At least 40 studies have documented the clinical utility of these CSF biomarkers in identifying AD. In ADNI, 89% of prodromal AD cases exhibited the AD biomarker profile [29], and other studies around the world have confirmed these results. A β ₄₂

levels are altered at least 5-10 years before conversion to AD, while t-tau and phospho-tau changes occur later in the disease process [30]. To this point, the European Medicines Agency (EMA) has qualified AD CSF biomarkers for prognostic use and enrichment in clinical trials [31] and Japan has approved CSF phospho-tau for diagnosis of dementia and t-tau for diagnosis of Creutzfeldt-Jakob Disease (CJD).

CSF biomarkers could also be useful in demonstrating proof of mechanism in clinical studies of disease-modifying drugs, which is now considered essential for drug development. For example, the gamma secretase inhibitor, semagacestat (LY 450139), was shown to lower CSF A β in a dose dependent fashion [32]. In pre-clinical studies, BACE1 inhibition was shown to induce a specific CSF biomarker profile in dogs, suggesting that biomarkers could be used as an indicator of pharmacodynamic effects [33]. Even when a drug fails to show a therapeutic benefit, biomarker data can often help to elucidate whether the drug hit its target or exerts off-target effects, which might convince a sponsor to continue pursuing development. When biomarkers are used to detect the effects of drugs, they may be called “theranostic biomarkers,” and are especially helpful because they can illuminate alternative pathological pathways [34]

The most common methods used for testing CSF biomarkers, particularly A β , phospho-tau and t-tau, are enzyme-linked immunosorbent assay (ELISA), Luminex xMap technology, and a multi-array technology introduced by Meso Scale Discovery. While ELISA A β , and tau values are generally of higher sensitivity than Luminex, both methods have similar diagnostic accuracy [35]. However, while single center studies with standardized protocols have shown good reproducibility, multicenter trials have shown that there is substantial center-to-center variation

[36]. Thus, if CSF A β and tau biomarker studies are to be used in multicenter clinical trials, there will have to be better standardization or protocols for both preanalytic (collection, handling, and storage of specimens) and analytic factors. To this end, the Alzheimer's Biomarker Standardization Initiative (ABSI), a European Union-United States consortium sponsored by Innogenetics has been working to build consensus on standardization of pre-analytic and analytic procedures and protocols [37], and the Alzheimer's Association established a collaborative international quality control program for AD CSF biomarkers [38]. These partnerships are not only investigating factors that contribute to variability, but also establishing procedures to reduce variability by alerting labs when there are outliers so that procedures can be revised if necessary; alerting producers to variability so that kit stability can be improved; providing hands on training; and providing certified reference materials. Ultimately, the regulatory authorities will require certification of any commercially marketed arrays as in vitro diagnostics (IVD). An International Standard (IS) will need to be prepared for use in Quality Assurance (QA) of the laboratories using the IVD through Quality Control (QC) and External Quality Assessment (EQA) programs.

There are also efforts to develop new CSF biomarkers, for example using proteomics and mass spectroscopy to assess various CSF A β isoforms [39], and developing assays to measure synaptic proteins. These newer technologies will be subject to the same need for standardization and will benefit from progress to date in this sphere.

3.5 Novel biomarkers

The discovery and development of accurate and sensitive blood or plasma-based biomarkers could have a profound effect on diagnosis and drug discovery since these approaches are amenable for population screening as a first approach for early disease detection or prognosis. AddNeuroMed, a collaboration of academic institutions throughout Europe, has been investigating a number of novel blood-based biomarkers, using both candidate and data-driven approaches. These studies have identified candidate biomarkers using genomics, proteomics, and transcriptomics technologies, which provide new insight into biological pathways involved in the disease. For example, transcriptomic studies have identified potential biomarkers that point to vesicle-mediated transport as an important pathway affected in AD patients, and gel-based proteomic studies have identified a protein signature in blood that appears promising [40]. In a recent AddNeuroMed study, a panel of five plasma proteins assessed by ELISA and Western blotting were shown to correlate with brain atrophy in AD patients [41]. A 30-40 protein panel is now being validated as an assay for AD. Similar projects to search for serum- and plasma-based biomarkers are underway through other consortia, including AIBL. Like CSF-based assays, serum- and plasma-based assays face similar pre-analytic and analytic standardization issues. Thus, an international working group called STAR-B (STAndards for Alzheimer's Research in Blood Biomarkers) has been created to address issues related to standardization and develop appropriate standards.

4.0 Combining assessments for accurate diagnosis

Since different biomarkers address different questions, multiple biomarkers are needed to fully describe the pathophysiology of AD. For example, a positive amyloid biomarker indicates a patient's disease path, while a positive biomarker of neurodegeneration (i.e., hippocampal

atrophy, elevated CSF tau, or hypometabolism on FDG-PET) indicates how close the patient is to a clinical endpoint, while not in itself indicating that the patient has AD.

With the current state of knowledge, amyloid imaging or CSF A β assessment is highly informative when it is negative, because it provides strong evidence that a patient's complaints are not due to Alzheimer's disease, and would likely not respond to an amyloid-based treatment; thus increasing the likelihood that the patient has a potentially treatable cause for the cognitive symptoms such as depression. A positive amyloid biomarker increases the likelihood that cognitive decline is due to AD, especially in young onset patients. Given that there is currently no amyloid-targeting treatment with demonstrated efficacy on the market, the cost-benefit ratio argues for restricted clinical use of these expensive tests. Once a successful treatment is identified, however, the balance may shift in the other direction. In addition, the importance of biomarkers in the development of such treatments is crucial and supported by the various federal regulatory agencies worldwide.

While biomarkers used in combination offer valuable clinical information, significant additional longitudinal data are needed to create reliable models that describe the full trajectories of AD biomarkers [42]. Such data should emerge over the next few years from ADNI, AIBL and other longitudinal studies.

5.0 Harmonizing reporting standards

In addition to standardizing and harmonizing the assessments themselves, reporting standards also need to be consistent across studies. The Alzheimer's Association recently initiated a

project called Global Alzheimer's Association Interactive Network (GAAIN, www.gaain.org) to provide researchers access to aggregated federated data across multiple projects, providing researchers with free-of-charge access to a vast repository of data – most importantly to high-resolution, time-varying, multidimensional data sets of the brain. GAAIN will feature sophisticated analytical tools and massive computational power that will enable researchers to ask and answer complex, previously unanswerable questions. Users can both work with data in the repository and share their own data. Software will also be developed to take advantage of cloud computing, harness cloud resources, and conduct analyses quickly. Importantly, GAAIN will utilize CADRO, the Common Alzheimer's Disease Research Ontology that was developed by the NIA and Alzheimer's Association to enable integration and comparative analysis of AD research portfolios across the public and private sectors around the world [43].

6.0 Qualification of biomarkers for clinical trials.

As noted earlier, regulatory agencies in Europe and Japan have already moved towards the qualification of biomarkers for use in AD clinical trials. The Coalition Against Major Diseases (CAMD), part of the Critical Path Initiative, is a consortium of member organizations from the pharmaceutical industry, global regulatory agencies, patient advocacy groups, research foundations, government funding agencies, academia, scientific associations, and consultant groups working collaboratively in pre-competitive space to advance therapies to treat neurodegenerative diseases. CAMD is thus advancing two biomarker approaches for enrichment in clinical trials through the FDA's biomarker qualification review process – one based on structural neuroimaging and one based on CSF analytes. This qualification program promotes a collaborative setting with multiple stakeholders working to develop drug development tools for

qualification. The process used is an iterative one with numerous opportunities for consortia to seek consultation along the way. The appeal of regulatory qualification is that by enabling acceptance and application of drug development tools across multiple drug development programs, drug development could proceed more efficiently.

The CAMD biomarker teams met with the FDA's Biomarker Qualification Review Team at the end of February, 2012 to seek advice on the comprehensive briefing document that each team submitted to the Agency at the end of 2011. The venue was collaborative and included attendees from the various divisions of the FDA as well as industry, regulatory and academic experts representing CAMD. Key themes discussed included application of the biomarker in drug development, assay analytical performance and standardization, confirmatory datasets to be analyzed, and statistical analysis plans.

7.0 Conclusions

The AD biomarker field has made tremendous advances in recent years in the development of both research and clinical tools. Participants at the RASAD conference agreed that continued progress requires increased standardization and harmonization of both preanalytic and analytic protocols as well as accelerated research on new biomarkers. Caution was urged, however, on too rapid acceptance of a universal standard until further results are available. Whilst consensus was reached on a number of issues raised, there were also any questions identified that remain to be addressed.

There was consensus that biomarkers may be useful in the clinic; however, RASAD participants agreed that use of a surrogate marker of AD in isolation is not yet realistic for diagnosis. While biomarkers for amyloid have high sensitivity and specificity for the presence of Alzheimer's related pathology, this may not fully explain a patient's presentation. Enrichment for clinical trials is a concept applied at the group level; however diagnosis is applied at individual level. Thus, while biomarkers may be used for enrichment even if confidence in their accuracy is low, much higher accuracy is needed to enable the use of biomarkers for diagnosis. Other points of agreement with regard to clinical use of biomarkers included:

- For clinical use, strict standardization is particularly important because physicians outside of expert centers may lack the knowledge needed to correctly interpret scans. Automated quantitation of all forms of imaging with comparison to normal databases should be encouraged. It will reduce variability in scan interpretation in clinical practice and may provide more precise prognostic and diagnostic information than a binary (positive or negative) report.
- Multiple biomarkers are needed to fully describe the pathophysiology of disease in an individual with dementia.
- Trying to dichotomize cases into AD or not AD can create problems for cases that are not classifiable using currently available tools.
- Expert centers using harmonized protocols should be encouraged to use biomarkers for clinical diagnosis so that we can learn about their use in daily practice.

RECOMMENDATIONS CAN BE POSTED IN NARRATIVE BOXES:

With regard to the uses of biomarkers in clinical trials, agreement was reached on the following points:

- All clinical trials should incorporate biomarkers for subject selection when the target is known and related to a biomarker (e.g. amyloid imaging or CSF A β for amyloid based therapies).
- A combination of demographic variables, neuroimaging and fluid biomarkers, and sensitive cognitive and functional measures will be needed to design efficient trials.
- Better biomarkers and standardization are extremely critical for powering studies and reducing the number of subjects needed. However screening for suitable subjects in itself may be very expensive. For example, the proposed Anti-Amyloid Treatment in Asymptomatic AD Trial (A4 study) plans to enroll 500 PiB-positive subjects per arm to achieve sufficient power to demonstrate clinical efficacy of treatment. It is important to note that over 3,000 subjects will need to be PiB screened to obtain the 1,000 for inclusion in the trial.
- When biomarkers are used to enrich subject populations in clinical studies, an early signal of efficacy is also valuable to ensure that the biomarker findings have clinical relevance.

Consensus on specific issues related to structural MR as an AD biomarker included:

- Validation of an automated algorithm and certification as a medical device are needed. One FDA certified program is commercially available that measures hippocampal volume and compares it to a normal database.

- A validated automated algorithm should be distributed by MR manufacturers to the medical community, followed by linkage to a normative database, establishment of an oversight committee without commercial bias, and credentialing of MR centers.

Amyloid imaging using PET scanning is already used extensively in clinical trials and is likely to become a widely used clinical tool, at least in resource rich countries. Consensus was reached on a number of points:

- When used as a clinical tool, a negative amyloid scan should raise questions about an AD diagnosis and lead to re-evaluation of the patient with particular attention to potentially reversible factors such as depression.
- However, if an amyloid imaging scan is negative, the individual may have low levels of AD-related pathology, since we know that there is a threshold for detecting amyloid plaques with the existing imaging agents.

Regarding the use of biomarkers in research, participants agreed that:

- Biomarkers are already available for testing some hypotheses about pathophysiology.
- We still do not understand the fundamental biology of AD; thus new biomarkers are needed, including measures of synaptic function.
- There is an ongoing need to bank blood and other biofluids for future studies to identify more biomarkers.
- Research and clinical studies should endeavor to track data such as tube numbers, lot numbers, etc. for post hoc analysis as new biomarkers or analytic tools become available.

While the RASAD conference reached substantial consensus on many issues regarding the standardization of biomarkers for clinical trials, diagnosis, and research, many questions remain to be addressed in the coming years. Perhaps the biggest question is how much precision and reproducibility, i.e., how much standardization is necessary. Other questions include:

- How should cut-points for various measures be established, and should they be used only for enrichment in clinical trials or as outcome measures?
- How representative are ADNI data, and will sponsors be able to use biomarkers validated with ADNI data?
- If biomarkers are used in clinical trials, is there a risk of the FDA requiring labeling linked to that biomarker?
- When biomarker and imaging studies are used in research studies, should subjects be informed of the results? Participants at the conference agreed that if the information affects medical management or if it confirms that a subject does not have AD, researchers would be justified in disclosing the information; however, any other disclosure would be problematic with the current level of knowledge regarding the meaning of biomarker results.
- How can the field prepare for the oncoming wide availability of biomarkers and amyloid imaging tests before there is a full understanding of their clinical and prognostic meaning?

Further work through international consensus committees is underway to improve research standardization in AD. A follow-up RASAD conference is planned in 2014, which will target the questions remaining from this conference and review progress and implementation of the various international standardization consortia.

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National Plan to Address Alzheimer's Disease



U.S. Department of Health and Human Services

National Plan to Address Alzheimer's Disease



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Introduction

Vision Statement

For millions of Americans, the heartbreak of watching a loved one struggle with Alzheimer's disease is a pain they know all too well. Alzheimer's disease burdens an increasing number of our Nation's elders and their families, and it is essential that we confront the challenge it poses to our public health.

-- President Barack Obama

National Alzheimer's Project Act

On January 4, 2011, President Barack Obama signed into law the National Alzheimer's Project Act (NAPA), requiring the Secretary of the U.S. Department of Health and Human Services (HHS) to establish the National Alzheimer's Project to:

- Create and maintain an integrated national plan to overcome Alzheimer's disease.
- Coordinate Alzheimer's disease research and services across all federal agencies.
- Accelerate the development of treatments that would prevent, halt, or reverse the course of Alzheimer's disease.
- Improve early diagnosis and coordination of care and treatment of Alzheimer's disease.
- Improve outcomes for ethnic and racial minority populations that are at higher risk for Alzheimer's disease.
- Coordinate with international bodies to fight Alzheimer's globally.

The law also establishes the Advisory Council on Alzheimer's Research, Care, and Services and requires the Secretary of HHS, in collaboration with the Advisory Council, to create and maintain a national plan to overcome Alzheimer's disease (AD).

NAPA offers a historic opportunity to address the many challenges facing people with Alzheimer's disease and their families. Given the great demographic shifts that will occur over the next 30 years, including the doubling of the population of older adults, the success of this effort is of great importance to people with AD and their family members, public policy makers, and health and social service providers.

Taking Immediate Action to Fight Alzheimer's Disease

Building on the preliminary work on this plan, on February 7, 2012, the Obama Administration announced a historic \$156 million investment to tackle Alzheimer's disease.

This investment includes:

Immediately increasing Alzheimer's disease research funding. The National Institutes of Health (NIH) immediately dedicated an additional \$50 million from its fiscal year 2012 funding to Alzheimer's disease research.

Sustaining and growing the Alzheimer's disease research investment. The President's fiscal year 2013 budget proposes \$80 million in new Alzheimer's disease research funding. Together, the fiscal years 2012 and 2013 investments would total \$130 million in new Alzheimer's disease research funding over two years.

Supporting people with Alzheimer's disease and their families and educating the public and providers. The initiative also includes \$26 million to support the goals of the National Plan, including:

- Education and outreach to improve the public's understanding of Alzheimer's disease
- Outreach to enhance health care providers' knowledge of the disease
- Expanded support for people with Alzheimer's disease and caregivers in the community
- Improved data collection and analysis to better understand the impact of Alzheimer's disease on people with the disease, families and the health and long-term care systems

This initiative aims to take immediate action on Alzheimer's disease without waiting for Congress to act. And, it provides support for ideas being developed through this National Plan.

The National Plan

This is the first National Plan. This plan includes a detailed listing of current federal activities and, as directed by NAPA, initial recommendations for priority actions to expand, eliminate, coordinate or condense programs. The activities outlined in this plan vary in scope and impact and include: (1) immediate actions that the federal government will take; (2) actions toward the goals that can be initiated by the federal government or its public and private partners in the near term; and (3) longer-range goals that will require numerous actions to achieve. This is a National Plan and not a federal plan. It will require the active engagement of public and private sector stakeholders to achieve. In the case of many of the long-range goals, the path forward will be contingent on resources, scientific progress, and focused collaborations across many partners. Over time, HHS will work with the Advisory Council and stakeholders to add additional transformative actions.

A critical part of optimizing resources is ensuring coordination of the implementation of the National Plan with implementation of other HHS-wide plans and strategies, including Multiple Chronic Conditions: A Strategic Framework (2010), the HHS Action Plan to Reduce Racial and Ethnic Health Disparities (2011), National Prevention Strategy (2011), and HHS Strategic Plan (2010-2015). Appendix 2 provides a crosswalk of the Goals and Strategies of this plan with the Goals, Objectives, and Strategies of these related efforts. The alignment of these plan components will facilitate progress across plans as they are each carried out.

Alzheimer's Disease

Alzheimer's disease is an irreversible, progressive brain disease that affects as many as 5.1 million Americans.¹ It slowly destroys brain function, leading to cognitive decline (e.g., memory loss, language difficulty, poor executive function), behavioral and psychiatric disorders (e.g., depression, delusions, agitation), and declines in functional status (e.g., ability to engage in activities of daily living and self-care).² In 1906, Dr. Alois Alzheimer first documented the disease when he identified changes in the brain tissue of a woman who had memory loss, language problems, and unpredictable behavior. Her brain tissue included abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary tangles). Brain plaques and tangles, in addition to the loss of connections between neurons, are the main features of AD.³

In this plan, the term "Alzheimer's disease," or AD, refers to Alzheimer's disease and related dementias, consistent with the approach Congress used in NAPA. Related dementias include frontotemporal, Lewy body, mixed, and vascular dementia. It is often difficult to distinguish between Alzheimer's disease and other dementias in terms of clinical presentation and diagnosis. Some of the basic neurodegenerative processes have common pathways. People with dementia and their families face similar challenges in finding appropriate and necessary medical and supportive care. Unless otherwise noted, in this plan AD refers to these conditions collectively.

The first symptom of AD is often memory impairment. As the disease progresses, memory continues to decline, and other functions like language skills and decision making become more difficult. Personality and behavior changes may also occur. A person with the disease may no longer recognize family and friends. Eventually, the person who survives with Alzheimer's disease is completely reliant on others for assistance with even the most basic activities of daily living, such as eating.^{4,5}

In more than 90 percent of people with Alzheimer's disease, symptoms do not appear until after age 60, and the incidence of the disease increases with age. The causes of AD are not completely understood, but researchers believe they include a combination of genetic, environmental, and lifestyle factors.⁶ The importance of any one of these factors in increasing or decreasing the risk of developing AD may differ from person to person. In rare cases, known as early or younger-onset AD, people develop symptoms of AD in their 30s, 40s, or 50s. A significant number of people with Down syndrome also develop dementia in their 50s.

AD is a major public health issue and will increasingly affect the health and well-being of the population. Unless the disease can be effectively treated or prevented, the number of Americans with AD will increase significantly in the next two decades. The number of people age 65 and older in the U.S. is expected to grow from 40 million in 2010 to 72.1 million in 2030. The prevalence of people with AD doubles for every 5-year interval beyond age 65. The significant growth in the population over age 85 that is estimated to occur between 2010 and 2030 (from 5.5 million to 8.7 million) suggests a substantial increase in the number of people with AD.

Alzheimer's disease places an enormous emotional, physical, and financial stress on individuals who have it and their family members. Informal caregivers, such as family members and friends, provide the majority of care for people with AD in the community. Informal caregivers often do not identify themselves as such; they are simply a wife, daughter, husband, son, or friend helping a person whom they care about. However, the intensive support required for a person with AD can negatively impact the caregiver's emotional and physical health and well-being. Informal caregivers often report symptoms of depression and anxiety, and have poorer health outcomes than their peers who do not provide such care.⁷ When the person with AD moves to a nursing home to receive 24-hour care, the financial costs to families are great: an estimated \$78,000 per year.⁸

Caring for people with Alzheimer's disease also strains the health and long-term care systems. Individuals with Alzheimer's disease use a disproportionate amount of health care resources; for instance, they are hospitalized 2-3 times as often as people the same age who do not have the disease.⁹ Similarly, while people living in nursing homes are a small percentage of the older population, nearly half (48%) of nursing homes residents have Alzheimer's disease.¹⁰ As the number of people with AD grows over the next two decades, this disease will place a major strain on these care systems as well as on Medicare and Medicaid, the major funders of this care.

The Challenges

This National Plan is designed to address the major challenges presented by Alzheimer's disease:

1. While research on AD has made steady progress, there are no pharmacological or other interventions to definitively prevent, treat, or cure the disease.
2. While HHS and other groups have taken steps to develop quality measures to assess Alzheimer's care and to improve the training of the health and long-term care workforce, there is room for improvement.

3. Family members and other informal caregivers, who take on the responsibility of caring for a loved one with AD, need support. The majority of people with AD live in the community, where their families provide most of their care. The toll of caregiving can have major implications for caregivers and families as well as population health, with about one-third of caregivers reporting symptoms of depression.^{11,12}
4. Stigmas and misconceptions associated with AD are widespread and profoundly impact the care provided to and the isolation felt by people with AD and their families.
5. Public and private sector progress is significant but should be coordinated and tracked. In addition, data to track the incidence, prevalence, trajectory and costs of AD are limited.

Framework and Guiding Principles

The enactment of NAPA creates an opportunity to focus the Nation's attention on the challenges of AD. In consultation with stakeholders both inside and outside of the federal government, this National Plan represents the initial blueprint for achieving the vision of a Nation free of AD.

Central to and guiding the National Plan are the people most intimately impacted by Alzheimer's Disease -- those who have the disease and their families and other caregivers. Individuals with AD and their caregivers receive assistance from both the clinical health care system and support systems such as long-term care, home care, legal services, and other social services. Both the clinical care and support environments need better tools to serve people with Alzheimer's disease and their caregivers. Ongoing and future research seeks to identify interventions to assist clinicians, supportive service providers, persons with AD, and caregivers. All of these efforts must occur in the context of improved awareness of the disease and its impacts and the opportunities for improvement. The National Plan aims to address these key needs. HHS is committed to tracking and coordinating the implementation of NAPA and making improvements aimed at achieving its ambitious vision.

The plan is also guided by three principles:

1. **Optimize existing resources and improve and coordinate ongoing activities.** The first step in developing the National Plan was to set up a federal interagency working group and conduct an inventory of all federal activities involving AD (Appendix 3). In creating the plan, HHS and its partners sought to leverage these resources and activities, improve coordination, and reduce duplication of efforts to better meet the challenges of Alzheimer's disease. The activities included in the inventory comprise ongoing work and new opportunities created by the Affordable Care Act. The federal working group process has already led to improved coordination and awareness throughout the federal government and set in motion commitments for further collaboration. Further, this process has allowed for identification of non-AD-specific programs and resources that may be leveraged to advance AD care.
2. **Support public-private partnerships.** The scope of the problem of Alzheimer's disease is so great that partnerships with a multitude of stakeholders will be essential to making progress. This National Plan begins the partnership process by identifying areas of need and opportunity. The plan relies on the Advisory Council in particular to identify key areas where public-private partnerships can improve outcomes.

3. ***Transform the way we approach Alzheimer’s disease.*** The National Plan represents a first step in an undertaking that will require large-scale, coordinated efforts across the public and private sectors. With principles 1 and 2 above, as well as the ambitious vision that the federal government is committing to through this National Plan, HHS and its federal partners seek to take the first of many transformative actions that will be needed to address this disease. Through an ongoing dialogue with the Advisory Council, the federal government will identify the most promising areas for progress and marshal resources from both within and outside the government to act on these opportunities.

Goals as Building Blocks for Transformation

Achieving the vision of eliminating the burden of Alzheimer’s disease starts with concrete goals. Below are the five that form the foundation of this National Plan:

1. Prevent and Effectively Treat Alzheimer’s Disease by 2025
2. Optimize Care Quality and Efficiency
3. Expand Supports for People with Alzheimer’s Disease and Their Families
4. Enhance Public Awareness and Engagement
5. Track Progress and Drive Improvement

Goal 1: Prevent and Effectively Treat Alzheimer's Disease by 2025

Research continues to expand our understanding of the causes of, treatments for, and prevention of Alzheimer's disease. This goal seeks to develop effective prevention and treatment modalities by 2025. Ongoing research and clinical inquiry can inform our ability to delay onset of Alzheimer's disease, minimize its symptoms, and delay its progression. Under this goal, HHS will prioritize and accelerate the pace of scientific research and ensure that as evidence-based solutions are identified they are quickly translated, put into practice, and brought to scale so that individuals with Alzheimer's disease can benefit from increases in scientific knowledge. HHS will identify interim milestones and set ambitious deadlines for achieving these milestones in order to meet this goal.

Key to advancing this goal is the Obama Administration's investment of \$50 million in new Alzheimer's disease research funding in fiscal year 2012 and \$80 million in new Alzheimer's disease research funding in fiscal year 2013. These investments will open new opportunities in Alzheimer's disease research and jumpstart efforts to reach the 2025 goal.

Strategy 1.A: Identify Research Priorities and Milestones

Research agencies undertake research planning processes on an ongoing basis, but a special effort is needed to identify the priorities and milestones to achieve Goal 1. The actions below will identify the priorities, establish milestones, and ensure that appropriate stakeholders are involved in the planning process aimed at minimizing Alzheimer's disease as a health burden by 2025. During the course of this work, NIH will develop research priorities, and a plan for implementing each phase of research in a coordinated manner. Coordination will occur across NIH Institutes and other Federal research agencies and with the private sector, as appropriate.

Action 1.A.1: Convene an Alzheimer's disease research summit with national and international scientists to identify priorities, milestones, and a timeline

In May 2012, the National Institute on Aging (NIA) of the National Institutes of Health will convene a research summit, Alzheimer's Research Summit 2012: Path to Treatment and Prevention, to provide expert input into identification of research priorities, to explore public and private research collaborations, and to establish strategies and milestones for an ambitious plan to slow progression, delay onset, and prevent Alzheimer's disease. The summit will include national and international experts in Alzheimer's disease and dementia research, public and private stakeholders, and members of the Advisory Council on Alzheimer's Research, Care, and Services. Summit proceedings will be open to the public.

Action 1.A.2: Solicit public and private input on Alzheimer's disease research priorities

HHS will continue to seek input and feedback from the public on its Alzheimer's disease research. Specifically, NIA will issue a Request for Information (RFI) to invite public and private input on funded research addressing Alzheimer's disease and related dementias.

Action 1.A.3: Regularly update the National Plan and refine Goal 1 strategies and action items based on feedback and input

HHS and its federal partners will use the input received through the Alzheimer's disease summit and the RFI to inform implementation of the National Plan. An updated Goal 1 will reflect the priorities, milestones, and timeline elements identified through these processes to accelerate research in this area. These will be incorporated into the next iteration of the National Plan and will be updated on an annual basis with the input of the Advisory Council.

Action 1.A.4: Convene a scientific workshop on other dementias in 2013

HHS will expand the work undertaken in Actions 1.A.1 and 1.A.2 to address non-Alzheimer's dementias. NIH will hold a scientific workshop in 2013 to solicit input on special research priorities and timelines for addressing related dementias.

Action 1.A.5: Update research priorities and milestones

To ensure that the research priorities and milestones reflect the broad input of the scientific community and the public, one Advisory Council meeting per year will be focused on this area. A relevant subcommittee focused on research or Goal 1 will collect input and recommend priorities and milestones for consideration by the Advisory Council as official recommendations. As appropriate, researchers in the field will also be invited to present at these meetings.

Strategy 1.B: Expand Research Aimed at Preventing and Treating Alzheimer's Disease

HHS and its federal partners will expand clinical trials on pharmacologic and non-pharmacologic ways to prevent Alzheimer's disease and manage and treat its symptoms. The federal government will address the challenge of enrolling enough people in clinical trials who are representative of the country's population, including ethnic and racial populations that are at higher risk for AD, through new partnerships and outreach. These actions will build on ongoing research focused on the identification of genetic, molecular and cellular targets for interventions and build on recent advances in the field.

Action 1.B.1: Expand research to identify the molecular and cellular mechanisms underlying Alzheimer's disease, and translate this information into potential targets for intervention

Incomplete understanding of the disease mechanisms that lead to AD is a major barrier to the discovery of effective therapies. An integrated interdisciplinary basic science research agenda will continue to advance our understanding of the molecular, cellular, and tissue level mechanisms and networks involved in the AD disease process to enable the identification and selection of therapeutic targets.

Action 1.B.2: Expand genetic epidemiologic research to identify risk and protective factors for Alzheimer's disease

NIH will undertake a new initiative to conduct whole genome sequencing to identify areas of genetic variation that correspond to increased risk (risk factors) or decreased risk (protective factors) of AD. This research is expected to yield novel targets for drug development, provide improved diagnostics for screening and disease monitoring, and ultimately help define strategies for disease prevention.

Action 1.B.3: Increase enrollment in clinical trials and other clinical research through community, national, and international outreach

Increased enrollment in clinical trials is crucial for the development of better treatments and ultimately a cure for AD. Participating in clinical trials and other research enables volunteers to access the latest experimental approaches available and provides them with care by clinical research staff. HHS will convene representatives from across the federal government, state and local governments, academic medical research institutions, and the private sector to create an action plan for increasing enrollment in clinical trials, including through the building of registries. The partners will identify approaches and coordination points for these efforts to implement the action plan.

Action 1.B.4: Monitor and identify strategies to increase enrollment of racial and ethnic minorities in Alzheimer's disease studies

NIH will monitor enrollment of racial and ethnic minorities in NIH Alzheimer's disease studies and work with other research funders to do the same. NIH will use this information to identify next steps for engaging and enhancing research participation by racial and ethnic minorities.

Action 1.B.5: Conduct clinical trials on the most promising pharmacologic interventions

HHS and the Department of Veterans Affairs (VA) will continue to develop and conduct clinical trials on the most promising pharmaceuticals for the prevention and treatment of Alzheimer's disease. NIA is a primary funder of large investigator-initiated clinical trials including the Alzheimer's Disease Cooperative Study (ADCS). Clinical trials will continue to advance the development of interventions and evaluate their effectiveness. HHS will increase the pace of work under its cooperative agreement with VA and other federal agencies to advance the progress of clinical trials. HHS will coordinate these efforts with those occurring in the private sector, as appropriate, by pursuing appropriate planning and research partnerships.

Action 1.B.6: Continue clinical trials on the most promising lifestyle interventions

HHS and its federal partners will continue to conduct clinical trials to test the effectiveness of lifestyle interventions and risk factor reduction in the prevention of AD, conduct peer review of new grant applications, perform annual reviews of ongoing studies, and work to identify emerging opportunities for the development of new interventions.

Strategy 1.C: Accelerate Efforts to Identify Early and Presymptomatic Stages of Alzheimer's Disease

Significant advances in the use of imaging and biomarkers in brain, blood, and spinal fluids have made it possible to detect the onset of Alzheimer's disease, track its progression, and monitor the effects of treatment in people with the disease. Without these advances, these neurodegenerative processes could only be evaluated in non-living tissues. Accelerated research will improve and expand the application of biomarkers in research and practice. These advances have shown that the brain changes that lead to Alzheimer's disease begin up to 10 years before symptoms.¹³ Identifying imaging and other biomarkers in presymptomatic people will facilitate earlier diagnoses in clinical settings, as well as aid in the development of more efficient interventions to slow or delay progression.

Action 1.C.1: Identify imaging and biomarkers to monitor disease progression

HHS will expand its work to identify imaging and biomarkers through the public-private Alzheimer's Disease Neuroimaging Initiative (ADNI). This partnership will help identify and monitor disease progression, even in the early stages before individuals show symptoms of the disease.

Action 1.C.2: Maximize collaboration among federal agencies and with the private sector

HHS will maximize the effectiveness of research findings in neuroimaging and biomarkers through partnerships, meetings, and conferences with the private sector, FDA, and other federal agencies. These collaborations will focus on how to translate findings into treatments and clinical practice, as well as help identify promising new areas of exploration.

Strategy 1.D: Coordinate Research with International Public and Private Entities

In order to facilitate communication and collaboration, build synergy, and leverage resources, it is imperative that research across nations and across funders be coordinated. The actions below will formalize the coordination process beyond HHS and the federal government and make research available to the public for input.

Action 1.D.1: Inventory Alzheimer's disease research investments

Beginning in 2012, HHS will build on an ongoing effort by NIA to complete, disseminate, maintain, and annually update an inventory of national and international Alzheimer's disease research investments. This inventory will inform and facilitate coordination among researchers, their organizations, and funders. NIA will use the Alzheimer's disease research ontology, recently developed in collaboration with the Alzheimer's Association, as a framework for collecting, organizing, and comparing the portfolios of national and international public and private Alzheimer's disease research funders. HHS will compile the portfolio information and make it available to the public through a searchable online database.

Action 1.D.2: Expand international outreach to enhance collaboration

HHS will expand outreach to international partners on Alzheimer's disease research. NIA will continue to collaborate with the Canadian Institutes of Health Research and the Research Councils of the United Kingdom and reach out to the additional eight countries that are developing Alzheimer's disease or dementia research plans. HHS will invite these colleagues and representatives of relevant international organizations, to meet and discuss ongoing research priorities, and to provide research project information and categorization for the inventory.

Strategy 1.E: Facilitate Translation of Findings into Medical Practice and Public Health Programs

Currently, promising research and interventions are published in the research literature and presented at scientific meetings. Additional steps are needed to highlight promising findings and to facilitate dissemination and implementation of effective interventions to the general public, medical practitioners, the pharmaceutical industry, and public health systems, quickly and accurately.

Action 1.E.1: Identify ways to compress the time between target identification and release of pharmacological treatments

HHS will convene a group to examine ways to speed up the processes for bringing pharmacological treatments to market, including: identifying and validating therapeutic targets; developing new interventions; testing efficacy and safety; and regulatory approval. The group will look at the current average time and will identify places where the timeline could be shortened. The group will include representatives from the Food and Drug Administration, the Office of the Assistant Secretary for Planning and Evaluation (ASPE), and NIH who will consult with academic researchers and representatives from the private sector.

Action 1.E.2: Leverage public and private collaborations to facilitate dissemination, translation, and implementation of research findings

HHS will expand its work to disseminate research findings. NIH will partner with other federal agencies to disseminate research findings to networks of providers and researchers. FDA will work with the pharmaceutical and medical device industries to clarify the types and characteristics of data needed for approval and clinical implementation. Other HHS and federal partners will form collaborations to promote the translation of evidence-based findings to community and practice settings. For example, the Administration on Aging (AoA) and NIH will continue their collaboration on translational research focused on helping older adults maintain their health and independence in the community. Additionally, AoA and CDC will build upon current collaborative efforts between public health and aging services networks to disseminate these findings. HHS will explore partnerships with stakeholder groups to facilitate further dissemination.

Action 1.E.3: Educate the public about the latest research findings

HHS, VA, and other federal agencies will expand their outreach efforts to more effectively inform the public about research findings, including results from clinical trials and studies regarding the non-pharmacological management of physical, cognitive, emotional, and behavioral symptoms. The NIA's Alzheimer's Disease Education and Referral (ADEAR) Center will continue its focus in this area, and work with AoA and the Centers for Disease Control and Prevention (CDC) to expand outreach to include the findings of studies that center on community and public health interventions.

Goal 2: Enhance Care Quality and Efficiency

Providing all people with Alzheimer's disease with the highest-quality care in the most efficient manner requires a multi-tiered approach. High-quality care requires an adequate supply of culturally-competent professionals with appropriate skills, ranging from direct-care workers to community health and social workers to primary care providers and specialists. High-quality care should be provided from the point of diagnosis onward in settings including doctor's offices, hospitals, people's homes and nursing homes. Care quality should be measured accurately and coupled with quality improvement tools. Further, care should address the complex care needs that persons with AD have due to the physical, cognitive, emotional, and behavioral symptoms of the disease and any co-occurring chronic conditions. High-quality and efficient care is dependent on smooth transitions between care settings and coordination among health care and long-term services and supports providers.

To educate health care providers on ways to better identify and treat Alzheimer's disease and its symptoms, the Obama Administration's Alzheimer's disease announcement includes a new \$6 million investment over two years for provider education and outreach. Provider training and awareness is essential to effectively detecting Alzheimer's disease and caring for people affected by this devastating disease.

Strategy 2.A: Build a Workforce with the Skills to Provide High-Quality Care

The workforce that cares for people with Alzheimer's disease includes health care and long-term services and supports providers such as primary care physicians; specialists such as neurologists, geriatricians, and psychiatrists; registered nurses and advanced practice nurses; community health workers; social workers; psychologists; pharmacists; dentists; allied health professionals; and direct-care workers like home health aides and certified nursing assistants, who provide care at home or in assisted living or nursing homes. These providers need accurate information about caring for someone with Alzheimer's disease including the benefits of early diagnosis, how to address the physical, cognitive, emotional, and behavioral symptoms of the disease, and how to assist caregivers as they cope with the physical and emotional aspects of their caregiving responsibilities. Physicians and other health care providers need information on how to implement the "detection of any cognitive impairment" requirement in the Medicare Annual Wellness Visit included in the Affordable Care Act. Major efforts by both VA and the Health Resources and Services Administration (HRSA), including expanded training opportunities created in the Affordable Care Act, support geriatric training for physicians, nurses, and other health workers.¹⁴ Enhanced specialist training is also needed to prepare these practitioners for the unique challenges faced by people with Alzheimer's disease. In addition, work is needed to expand the capacity of the primary care community to serve people with Alzheimer's disease. Dementia-specific capabilities within the direct-care workforce need to be expanded and enhanced. The actions below will facilitate AD-specific training for care professionals in order to strengthen a workforce that provides high-quality care to people with Alzheimer's disease.

Action 2.A.1: Educate health care providers

HHS will undertake a comprehensive provider education effort targeting health care providers such as physicians, nurses, direct care workers and other professionals. The effort will be carried out through HRSA's Geriatric Education Centers and will focus on educating providers about Alzheimer's disease. It will include the latest clinical guidelines and information on how to work with people with the disease and their families. Health care providers will learn how to manage the disease while coordinating care in the context of other health conditions, and how to link people to support services in the community. Training will also discuss signs of caregiver burden and depression that providers should recognize and address. Health care providers will also be trained on the tools available to detect cognitive impairment and appropriate assessment processes for diagnosis of AD. These are being developed through a Centers for Medicare and Medicaid Services (CMS), NIA, and CDC collaboration to help providers detect cognitive impairment during office visits, such as the Medicare Annual Wellness Visit.

Action 2.A.2: Encourage providers to pursue careers in geriatric specialties

HHS will enhance three programs that encourage providers to focus on geriatric specialties. The Comprehensive Geriatric Education Program, as mandated by the Affordable Care Act, provides traineeships to support students pursuing advanced degrees in geriatric nursing, long-term services and supports, and gero-psychiatric nursing. In addition, HRSA will continue to support training projects that provide fellowships for individuals studying to be geriatricians, geriatric dentists, or geriatric psychiatrists. These programs prepare professionals to address the needs of people with Alzheimer's disease through service rotations in different care settings. HRSA will also continue to support the career development of geriatric specialists in academia through the Geriatric Academic Career Awards Program. Currently 65 percent of these awardees provide interprofessional clinical training on Alzheimer's disease.

Action 2.A.3: Collect and disseminate dementia-specific guidelines and curricula for all provider groups across the care spectrum

HHS will create and market a clearinghouse of dementia curricula and practice recommendations for providers across the care continuum, including physicians, nurses, social workers, psychologists, other health care professionals, direct-care workers, and informal caregivers. The clearinghouse will be hosted on a publicly-available website and updated regularly. HHS will seek expert input from public and private entities in developing the clearinghouse and ensure that its content incorporates existing evidence-based guidelines.

Action 2.A.4: Strengthen the direct-care workforce

HHS will strengthen the nursing home direct-care workforce through new training focused on high-quality, person-centered care for people with AD. This program was established by Congress in the Affordable Care Act. The training will be released in Spring 2012, and will be available to all nursing homes to share with their staff. This training will be available for both new and established aides.

Action 2.A.5: Strengthen state aging and public health workforces

HHS will coordinate with states to develop aging and public health workforces that are AD-capable and culturally competent. AoA will ask states to specify strategies to improve the AD-capability of the workforce in their State Aging Plans and relevant grant applications. These strategies may include enhancing Alzheimer's disease competencies among Aging Network staff, developing AD-capable community health and long-term care Options Counseling in Aging and Disability Resource Centers, and linking State Long-Term Care Ombudsmen programs to AD-specific training and resources. CDC will work with its partners to identify public health contributions at the state and local levels and continue to work with AoA on enhancing the interface of the aging and public health networks.

Action 2.A.6: Support state and local Alzheimer's strategies

Much of the work required to support caregivers and the direct-care workforce should and will occur at the local level. This is reflected in the many state-based plans to tackle Alzheimer's disease.¹⁵ Thus, HHS and its federal government partners will identify ways that are most helpful to support states and localities in their efforts such as conducting research and translating successful interventions that address management of AD symptoms, and supports for paid and unpaid caregivers. HHS will disseminate information about these interventions, and share best practices.

Strategy 2.B: Ensure Timely and Accurate Diagnosis

Far too many people with Alzheimer's disease are not diagnosed until their symptoms have become severe.¹⁶ Timely diagnosis gives people with the condition and their families time to plan and prepare for the future, leading to more positive outcomes for both.^{17,18} For many, the inability to access health care due to a lack of insurance is a major concern. This is particularly important for individuals with younger-onset disease who may not yet be eligible for Medicare. Much of that insecurity will be alleviated as the Affordable Care Act, with its elimination of pre-existing conditions limitations and expansion of insurance coverage, is implemented. Even with access to affordable care for individuals, the health care workforce needs tools that can help ensure timely and accurate diagnoses. Research has helped identify some assessment tools that can be used to detect cognitive impairment that may indicate the need for a comprehensive diagnostic evaluation for Alzheimer's disease.¹⁹ The actions below will facilitate appropriate assessment and give healthcare providers tools to make timely and accurate diagnoses.

Action 2.B.1: Link the public to diagnostic and clinical management services

Family members and loved ones are often the first to notice symptoms of AD and report their concerns to medical professionals. Thus, public awareness of the potential symptoms of Alzheimer's disease is important for detecting AD and ensuring a timely, accurate diagnosis. Once warning signs are identified, people with these symptoms and their families need access to formal diagnostic and support services. To that end, HHS will expand linkages between its disease support and community information centers supported by NIH and AoA. NIH's Alzheimer's Disease Education and Referral (ADEAR) Center will continue to educate the public and providers about the latest evidence on the symptoms of AD and current methods of diagnosing the disease. AoA's National Alzheimer's Call Center will work with the Aging Network to help connect families and people with symptoms of AD with AD-capable resources, including diagnostic services through NIH-funded Alzheimer's Disease Centers when available.

Action 2.B.2: Identify and disseminate appropriate assessment tools

The Affordable Care Act created the Medicare Annual Wellness Visit. "Detection of any cognitive impairment" must be included as part of the wellness visit. HHS is using research findings to identify the most appropriate assessment tools that can be used in a variety of outpatient clinical settings to assess cognition. The recommended tools will be distributed to practitioners to aid in identification and evaluation of cognitive impairment. Once cognitive impairment has been detected, practitioners will be able to consider potential causes of cognitive impairment and determine the need for a comprehensive diagnostic evaluation for AD.

Strategy 2.C: Educate and Support People with AD and Their Families upon Diagnosis

Often, even though a physician or another health care provider has identified cognitive impairment, the patient and his or her family are not told of the diagnosis.²⁰ Further, once a diagnosis is made and disclosed, as few as half of patients and families receive counseling, support, or information about next steps.²¹ This information is important, especially for early-stage patients who experience positive outcomes when they are involved in planning and receive appropriate services.²² The actions below will address this gap by educating physicians and other health care providers, incentivizing discussions with people with AD and their families, and enhancing the ability of other networks to assist people with Alzheimer's disease and their families with addressing their needs.

Action 2.C.1: Educate physicians and other health care providers about accessing long-term services and supports

One barrier to counseling and support is that health care providers are not aware of available services or how to access them. To increase knowledge of these resources among doctors, nurses, and hospitals, HHS will work with its federal partners, public and private entities, and the health care provider community to identify steps to effectively educate physicians and other health care providers about support resources and services available to assist people with AD and their caregivers. This work will be coordinated with the provider education effort in Action 2.A.1.

Action 2.C.2: Enhance assistance for people with AD and their caregivers to prepare for care needs

Outside of the clinical-care setting, families and people with AD need specialized assistance in planning for AD-specific needs and accessing appropriate services. HHS will work to strengthen the ability of existing long-term services and supports systems, such as those provided by AoA's Aging Network, to meet the unique needs of people with AD and their caregivers. HHS will strengthen the Aging Network's awareness of available family caregiver assessment tools, resource materials from across the government, and support programs designed to educate caregivers and persons with the disease.

Strategy 2.D: Identify High-Quality Dementia Care Guidelines and Measures Across Care Settings

Guidelines for delivery of high-quality care and measures of quality are needed to ensure people with Alzheimer's disease receive high-quality, culturally-competent care in the many different settings where they receive services. These guidelines should be tailored to the stages of the disease, address the physical, cognitive, emotional, and behavioral symptoms of AD, and cover the myriad care settings in which care is delivered. These guidelines should also take into account how care might be modified for diverse populations and in the context of co-occurring chronic conditions in people with AD. HHS will seek expert input from public and private entities and ensure that content builds on existing, evidence-based guidelines. Quality measures should be based on such guidelines and track whether recommended care is being provided. Guidelines and measures need to be free of conflicts of interest. The actions below will advance the development of guidelines and measures of high-quality care, as well as the ability of the provider community to improve the quality of the care they provide.

Action 2.D.1: Explore dementia care guidelines and measures

HHS will work with private partners to facilitate groups such as medical professional societies and organizations representing persons with AD, caregivers, and direct care workers working together to delineate best dementia care practices and evidence-based guidelines. This work can serve to inform clinical, behavioral health, and long-term services and supports providers, families, and people with AD, and can also serve as a foundation to guide the identification and development of metrics that promote high-quality dementia care in all settings.

Strategy 2.E: Explore the Effectiveness of New Models of Care for People with AD

The Affordable Care Act created the CMS Center for Medicare and Medicaid Innovation (CMMI) which is charged with testing innovative payment and service delivery models to reduce expenditures in Medicare and Medicaid while maintaining or enhancing the quality of care received by program beneficiaries. While these studies are not designed to focus on people with AD in particular, a number of the initiatives underway at CMMI may provide information relevant to the care for people with Alzheimer's disease. The Secretary can expand the duration and scope of care models that are shown to reduce spending and improve quality, including implementing them at a national level. Through the actions below, HHS will leverage the efforts that are already underway at CMMI as potential new AD-specific initiatives are identified.

Action 2.E.1: Evaluate the effectiveness of medical home models for people with AD

Medical homes utilize a team approach to provide care and to improve the quality and coordination of health care services. CMMI is currently carrying out the Multi-payer Advanced Primary Care Practice Demonstration and the Comprehensive Primary Care initiative to measure the effectiveness of medical home models. CMMI will conduct subgroup analyses to examine changes in care quality and care coordination among people with AD to explore whether these models lead to more effective and efficient care.

Action 2.E.2: Evaluate the effectiveness of the Independence at Home Demonstration

The Independence at Home Demonstration is testing a payment and service system that uses physicians and nurse practitioners to coordinate home-based primary care with long-term services and supports. CMMI will conduct subgroup analyses to examine whether health and functional status outcomes are improved among people with AD in this demonstration.

Strategy 2.F: Ensure that People with AD Experience Safe and Effective Transitions between Care Settings and Systems

People with dementia have higher rates of emergency room visits and hospitalizations, two settings where they are vulnerable to stress, delirium, and unnecessary complications. A transition between providers and care settings is a complex time of care delivery for all people, but especially for frail elders or other individuals with Alzheimer's disease who often have multiple chronic conditions. Transitions include moves into acute-care hospitals, from hospitals to post-acute settings such as skilled nursing facilities or the home, or from nursing facilities to hospitals. People with AD are at high risk of adverse events due to poor communication and other care process deficiencies during transitions and need support to help them determine the best timing for transition and site of care.²³

Action 2.F.1: Identify and disseminate models of hospital safety for people with AD

The Partnerships for Patients is a public-private partnership that helps improve the quality of care and safety in hospitals. Through this initiative, hospitals will identify best practices for reducing injuries, complications, and improving care transitions. CMMI will identify practices that benefit people with complex needs including people with Alzheimer's disease. CMS will share these findings broadly.

Action 2.F.2: Implement and evaluate new care models to support effective care transitions for people with Alzheimer's disease

HHS will examine how to improve care during transitions for people with Alzheimer's disease through Medicare's Community-Based Care Transitions Program and the Aging and Disabilities Resource Center (ADRC) Evidence-Based Care Transitions Program. Medicare's Community-Based Care Transitions Program is an ongoing demonstration that links hospitals with community-based organizations to encourage shared quality goals, improve transitions, and optimize community care. The ADRC Evidence-Based Care Transitions program supports state efforts to strengthen the role of ADRCs in implementing evidence-based care transition models that meaningfully engage older adults, individuals with disabilities, and their informal caregivers.

Strategy 2.G: Advance Coordinated and Integrated Health and Long-Term Services and Supports for Individuals Living with AD

Coordinating the care received by people with Alzheimer's disease in different settings by different providers can help reduce duplication and errors and improve outcomes.²⁴ Despite a general consensus that care coordination is important, more research is needed to determine how best to provide such care in a high-quality and cost-efficient manner. The actions under this strategy will focus on learning from the existing evidence regarding care coordination and using this information to implement and evaluate care coordination models for people with AD.

Action 2.G.1: Review evidence on care coordination models for people with Alzheimer's disease

HHS will convene federal partners and outside experts to review the research on care coordination models for people with Alzheimer's disease. This review will include an in-depth examination of promising models of care to help identify key components that improve outcomes for people with AD. HHS will also review the evidence comparing the effectiveness of structures, processes, and interventions on health, psychosocial, and functional outcomes of people with AD in long-term care settings and their caregivers.

Action 2.G.2: Implement and evaluate care coordination models

HHS will support states in developing new approaches to better coordinate care for people who are enrolled in both Medicare and Medicaid, many of whom have cognitive impairments. CMS has established a new technical assistance resource center, the Integrated Care Resource Center, authorized under the Affordable Care Act, to assist states in designing and delivering coordinated health care to beneficiaries. HHS will evaluate the impact of these models. The CMS Center for Medicare and Medicaid Innovation, in partnership with the CMS Medicare-Medicaid Coordination Office, provides an opportunity to test and evaluate promising models of care for people with AD.

Strategy 2.H: Improve Care for Populations Disproportionally Affected by Alzheimer's Disease and for Populations Facing Care Challenges

Some populations are unequally burdened by Alzheimer's disease, including racial and ethnic minorities and people with intellectual disabilities. Racial and ethnic minorities are at greater risk for developing Alzheimer's disease and face barriers to obtaining a diagnosis and services after onset. People with Down syndrome almost always develop AD as they age. In addition, because AD primarily affects older adults, the population with younger-onset AD faces unique challenges with diagnosis, care, and stigma. HHS will undertake the actions below to better understand the unique challenges faced by these groups and create a plan for improving the care that they receive, which will be integrated into the broader efforts to improve care for all people with AD.

Action 2.H.1: Create a taskforce to improve care for these specific populations

HHS will convene one or more groups of experts, both within and outside of the government, to take steps to address the unique care challenges faced by people with younger-onset Alzheimer's disease, racial and ethnic minorities, and people with Down syndrome and other intellectual disabilities. This group will focus on how to improve accurate and timely diagnosis, access to care, education on AD for practitioners who do not normally specialize in care for people with AD, and special considerations for these populations.

Action 2.H.2: Identify steps to ensure access to long-term services and supports for younger people with AD

The Administration on Aging (AoA), Office on Disability, and Administration on Developmental Disabilities (ADD) will work together to address access to long-term services and supports for younger people, including people with Down syndrome and other intellectual disabilities who develop AD early and people with younger-onset AD. Together these agencies will identify barriers to these supports and make recommendations to the Advisory Council and HHS on ways to address these barriers.

Goal 3: Expand Supports for People with Alzheimer’s Disease and Their Families

People with Alzheimer’s disease and their families need supports that go beyond the care provided in formal settings such as doctor’s offices, hospitals, or nursing homes. Families and other informal caregivers play a central role. Supporting people with Alzheimer’s disease and their families and caregivers requires giving them the tools that they need, helping to plan for future needs, and ensuring that safety and dignity are maintained. Under this goal, the federal government and partners will undertake strategies and actions that will support people with the disease and their caregivers.

To help respond to the challenges faced by families and other caregivers, the Obama Administration’s Alzheimer’s disease announcement proposes a new investment of \$10.5 million in fiscal year 2013 to support the needs of caregivers of people with Alzheimer’s disease.

Strategy 3.A: Ensure Receipt of Culturally Sensitive Education, Training, and Support Materials

Caregivers report that they feel unprepared for some of the challenges of caring for a person with Alzheimer’s disease -- for example, caring for a loved one with sleep disturbances, behavioral changes, or in need of physical assistance can be an enormous challenge.²⁵ Giving caregivers the information and training that they need in a culturally sensitive manner helps them better prepare for these and other challenges. The actions to achieve this strategy include identifying the areas of training and educational needs, identifying and creating culturally-appropriate materials, and distributing these materials to caregivers.

Action 3.A.1: Identify culturally sensitive materials and training

HHS will review culturally sensitive AD resources and identify areas where new resources need to be developed. HHS and private entities will develop relevant new culturally sensitive AD resources as needed.

Action 3.A.2: Distribute materials to caregivers

HHS will work with its agencies, other federal departments, and state and local networks and tribal governments to distribute training and education materials. This will include dissemination through the Aging Network, the public health network, and public websites.

Action 3.A.3: Utilize health information technology for caregivers and persons with AD

Reports from the National Research Council have reinforced the need for health information technology (HIT) applications for caregivers as well as people with AD and providers.^{26,27} Many opportunities exist for using technology to support people with AD and their caregivers. Opportunities include assistance with reminders, communications, and monitoring. HHS will identify an agenda for priority actions to support the use of technology to assist caregivers and persons with the disease.

Strategy 3.B: Enable Family Caregivers to Continue to Provide Care while Maintaining Their Own Health and Well-Being

Even though informal caregivers usually prefer to provide care to their loved ones in their home or other community settings, eventually the round-the-clock care needs of the person with AD may necessitate nursing home placement. While they are providing care, supports for families and caregivers can help lessen feelings of depression and stress and help delay nursing home placement.^{28,29,30} The actions below will further support informal caregivers by identifying their support needs; developing and disseminating interventions; giving caregivers information they need, particularly in crisis situations; and assisting caregivers in maintaining their health and well-being.

Action 3.B.1: Identify unmet service needs

HHS will analyze surveys and datasets, such as the Caregiver Supplement to the National Health and Aging Trends Study, to identify the service needs of caregivers of people with AD. These findings will be published and disseminated to federal partners and the public. HHS will also meet with state and local officials and stakeholders to discuss unmet needs in their communities.

Action 3.B.2: Identify and disseminate best practices for caregiver assessment and referral through the long-term services and supports system

While most states conduct caregiver assessments through their long-term services and supports system, there is not consistent information about best practices in caregiver assessment. HHS will explore a public-private partnership to identify best practices in caregiver assessment and referral. This effort will examine caregiver assessment tools used in states, including those used in state Medicaid waiver programs. Best practices related to caregiver assessment will be disseminated.

Action 3.B.3: Review the state of the art of evidence-based interventions that can be delivered by community-based organizations

HHS will partner with private organizations to convene a meeting of leading scientists and practitioners to review the state of the art of research and translational activities related to evidence-based interventions that can be delivered by community-based organizations. The meeting will be focused on interventions that have been effective in improving the health and well-being of persons with Alzheimer's disease and their caregivers. The outcome of the meeting will be a white paper outlining strategies for identifying promising interventions for research, translation, and expansion into practice at the community level.

Action 3.B.4: Develop and disseminate evidence-based interventions for people with Alzheimer's disease and their caregivers

HHS will expand its support for research and conduct trials, systematic reviews, and demonstration projects for evidence-based interventions to support individuals with Alzheimer's disease and their caregivers, work to identify emerging opportunities for the development of new interventions, and translate and disseminate findings immediately.

Action 3.B.5: Provide effective caregiver interventions through AD-capable systems

AoA will expand efforts to develop more AD-capable long-term services and supports systems designed to meet the needs of AD caregivers. Through these efforts, AoA will work with lead state agencies across state government and with the Aging Network to identify and address caregivers' needs when they seek assistance from state or local home and community-based services systems for themselves or for the person with AD. Caregivers will be connected to supportive services such as respite care. Caregivers will be linked to interventions shown to decrease burden and depression among caregivers and enhance the care received by people with Alzheimer's disease. As additional effective interventions are identified, HHS will work with its partners on implementation in appropriate settings.

Action 3.B.6: Share lessons learned through VA caregiver support strategies with federal partners

VA has a number of programs which support caregivers of Veterans, including the Caregiver Support Program, REACH-VA, Home-Based Primary Care, other in-home care and community-based services, and respite care. VA officials will share the lessons learned from implementing these programs and examining their impact on both caregivers and people with AD with other federal representatives through scheduled informational meetings.

Action 3.B.7: Support caregivers in crisis and emergency situations

AoA's National Alzheimer's Call Center provides expert advice, care consultation, information, and referrals at the national and local levels regarding Alzheimer's disease. Services include crisis counseling and detailed follow-through to ensure consumers receive appropriate and high-quality responses to their concerns. AoA and NIA, working with the National Alzheimer's Call Center and the Alzheimer's Disease Education and Referral (ADEAR) Center, will develop and present a webinar for the Aging Network, NIA-funded Alzheimer's Disease Centers, other federal partners highlighting the availability of the National Alzheimer's Call Center to support caregivers in crisis and disaster situations.

Strategy 3.C: Assist Families in Planning for Future Care Needs

The vast majority of people do not think about or plan for the long-term services and supports they will need until they experience a disability or AD. Many Americans incorrectly believe that Medicare will cover most of the costs of these supportive services.^{31,32} Unfortunately, by the time care is needed, it is difficult to get coverage in the private long-term care insurance market, and options are limited.³³ Educating people about their potential need for long-term services and supports and the significant advantages of planning ahead for these services encourages timely preparation. Planning ahead can help ensure that individuals with AD receive care in the setting they prefer and that their dignity is maintained.

Action 3.C.1: Examine awareness of long-term care needs and barriers to planning for these needs

HHS is working to better understand why middle-aged adults do or do not plan for long-term care needs. HHS will conduct a national survey to examine attitudes toward long-term care. It will also identify barriers to long-term care planning.

Action 3.C.2: Expand long-term care awareness efforts

HHS will expand public knowledge of the risks of Alzheimer's disease and the implications for future care needs through the Long-Term Care Awareness Campaign. Since 2005, the Campaign has been making individuals and families more aware of their potential need for long-term services and supports and the significant advantages of planning ahead. HHS will incorporate information about Alzheimer's disease into its materials for the Campaign.

Strategy 3.D: Maintain the Dignity, Safety and Rights of People with Alzheimer's Disease

People with Alzheimer's disease are particularly vulnerable to financial exploitation, physical or emotional abuse, and neglect both at home and in care facilities.³⁴ Reports of elder abuse are handled by state Adult Protective Services (APS), which investigate allegations, provide protective services, and refer cases to law enforcement when appropriate. Not all APS programs cover residents of long-term care facilities. State survey and certification agencies receive funding from CMS to survey Medicare or Medicaid-certified nursing facilities and to investigate abuse complaints in these facilities. State licensing agencies may investigate complaints of abuse in other types of facilities, such as assisted living. State Long-Term Care Ombudsman programs advocate for residents of nursing homes and other adult care facilities, and work to resolve complaints on behalf of residents, including those related to abuse, neglect, and exploitation. The actions below will help ensure that people with AD have their dignity, safety, and rights maintained.

Action 3.D.1: Educate legal professionals about working with people with Alzheimer's disease

HHS will work to educate legal service professionals about the vulnerabilities of people with Alzheimer's disease and how to most effectively serve this population by developing and providing AD-specific training through AoA's National Legal Resource Center (NLRC).

Action 3.D.2: Monitor, report and reduce inappropriate use of anti-psychotics in nursing homes

HHS has identified the inappropriate use of some medications, including anti-psychotic drugs, to manage difficult behaviors of nursing home residents, many of whom have Alzheimer's disease. CMS is leading a collaborative effort to reduce inappropriate and off-label use of antipsychotic and behavior modifying agents in nursing homes. This will be achieved through a multifaceted approach that includes updated surveyor guidance, stricter enforcement of rules, efforts to eliminate conflicts of interest by pharmacists, and, in partnership with the Alzheimer's Disease Education and Referral (ADEAR) Center, education of providers, prescribers, surveyors and families.

Strategy 3.E: Assess and Address the Housing Needs of People with AD

Stable housing is essential to helping people with Alzheimer's disease remain in the community, particularly as they experience an increasing need for services and supports as the disease progresses. Housing is a crucial platform for delivering the necessary health and supportive services. Recognizing these links, HHS and the Department of Housing and Urban Development (HUD) are working together to improve health outcomes and housing stability through supportive services for vulnerable populations including people with AD. Through the actions below, HHS will assess the availability of services in the settings where people with Alzheimer's disease live. This information will form the basis of future actions to further link housing with services for people with AD.

Action 3.E.1: Explore affordable housing models

HUD and HHS will explore models of affordable housing that provide coordinated housing, health and long-term services and supports for individuals as they age in the community. This work will include examining housing sites that link health and long-term services and supports. In addition, the project will link HUD and HHS data to understand the older adult population in HUD housing, including their health care utilization.

Action 3.E.2: Examine patterns of housing and services

HHS will undertake analyses of existing studies and surveys to better understand where people with Alzheimer's disease live and the availability of services in these settings. This will include an in-depth analysis of the National Survey of Residential Care Facilities to better understand the level of cognitive impairment among residents and the types of services provided in assisted living facilities. The results of these studies will be used to identify areas that the National Plan should address in future years.

Goal 4: Enhance Public Awareness and Engagement

Most of the public is aware of Alzheimer's disease; more than 85 percent of people surveyed can identify the disease and its symptoms. Alzheimer's disease is also one of the most-feared health conditions. Yet there are widespread and significant public misperceptions about diagnosis and clinical management.³⁵ Misperceptions lead to delayed diagnosis and to people with the disease and their caregivers feeling isolated and stigmatized. Enhancing public awareness and engagement is an essential goal because it forms the basis for advancing the subsequent goals of the National Plan. A better understanding of Alzheimer's disease will help engage stakeholders who can help address the challenges faced by people with the disease and their families. These stakeholders include a range of groups such as health care providers who care for people with AD and their caregivers, employers whose employees request flexibility to care for a loved one with the disease, groups whose members are caregivers, and broader aging organizations. The strategies and actions under this goal are designed to educate these and other groups about the disease.

The Obama Administration's Alzheimer's disease announcement invests \$8.2 million over two years, beginning this year, to support public awareness and to improve public knowledge and understanding of Alzheimer's disease.

Strategy 4.A: Educate the Public about Alzheimer's Disease

Greater public awareness of AD can encourage families to seek assessment, reduce isolation and misunderstanding felt by caregivers, and help link people in need to accurate information, resources and services.

Action 4.A.1: Design and conduct a national education and outreach initiative

HHS will design a multifaceted public awareness, outreach, and education initiative. The initiative will be carried out in collaboration with federal partners, states, local governments, and non-governmental entities. Formative research on population targets and the perceptions of diverse populations regarding AD will inform the initiative.

Strategy 4.B: Work with State, Tribal, and Local Governments to Improve Coordination and Identify Model Initiatives to Advance Alzheimer's Disease Awareness and Readiness across the Government

State, tribal, and local governments are working to help address challenges faced by people with Alzheimer's disease and their caregivers. Nineteen states and a handful of local entities have published plans to address AD that cover many of the same issues as the National Plan. Leveraging the available resources and programs across these levels of government will aid in the success of these efforts.

Action 4.B.1: Convene leaders from state, tribal, and local governments

HHS will convene national leaders from state, tribal, and local government organizations to identify steps for increasing AD awareness and readiness in their jurisdictions. These leaders will create an agenda for partnering and supporting the efforts described in this National Plan. HHS will engage key stakeholders from a range of constituencies whose participation is important for the success of this effort.

Action 4.B.2: Continue to convene federal partners

The Interagency Group on Alzheimer's Disease and Related Dementias, convened on an ongoing basis since April 2011, provides a forum for discussion of AD efforts across federal departments and agencies. Participants in this group have gained a better understanding of the roles and responsibilities of other departments and agencies for addressing Alzheimer's disease. Together, the group has identified existing resources and new opportunities for collaboration, best practices, and initiatives. HHS will continue to convene federal partners to collaborate on Alzheimer's disease. The group will share research findings, innovative or best practices, and information about new or upcoming initiatives.

Strategy 4.C: Coordinate U.S. Efforts with Those of the Global Community

Many nations have developed Alzheimer's plans of their own that involve improved care and supports for people with Alzheimer's disease and their caregivers, as well as enhanced research and public awareness. In implementing the actions in this plan, HHS and its federal partners will coordinate with global partners to enhance these plans, avoid duplication of effort, and optimize existing resources.

Action 4.C.1: Work with global partners to enhance collaboration

HHS will expand outreach to international partners on Alzheimer's disease through its Office of Global Affairs and other relevant federal agencies. HHS will invite colleagues and representatives of other countries and international organizations to meet and discuss ongoing Alzheimer's disease plans. These meetings will focus on shared research agendas, recent research findings, best practices in care across the continuum, and supports for informal caregivers.

Goal 5: Improve Data to Track Progress

The federal government is committed to better understanding AD and its impact on people with the disease, families, the health and long-term care systems, and society as a whole. Data and surveillance efforts are paramount to tracking the burden of AD on individual and population health and will be used to identify and monitor trends in risk factors associated with AD, and assist with understanding health disparities among populations such as racial and ethnic minorities. HHS will make efforts to expand and enhance data infrastructure and make data easily accessible to federal agencies and other researchers. This data infrastructure will help HHS in its multi-level monitoring and evaluation of progress on the National Plan.

The Obama Administration's Alzheimer's disease announcement responds to this goal with a proposal to invest \$1.3 million in fiscal year 2013 to improve data collection to better understand Alzheimer's disease's impact on people with the disease, their families and the health care system.

Strategy 5.A: Enhance the Federal Government's Ability to Track Progress

The federal government needs improved data on people with Alzheimer's disease, their caregivers, and the care and supports that they use to address policy questions and plan and evaluate new initiatives. HHS and its partners will identify the policy questions that cannot be answered with existing data, as well as questions likely to arise in the future. These questions will provide a mechanism for identifying gaps, challenges, and changes or additions to data collection.

Action 5.A.1: Identify major policy research needs

HHS will convene federal partners to identify current and future policy research questions that cannot be answered with existing data. Some topics this group will discuss include Medicare and Medicaid expenditures among people with Alzheimer's disease, as well as the impact of caregiver supports on health outcomes. The partners will identify gaps in data to evaluate progress on the National Plan that should be addressed.

Action 5.A.2: Identify needed changes or additions to data

HHS will work with federal partners and researchers to identify the data and data infrastructure needed to address the policy issues identified in Action 5.A.1. These changes or additions may include new or improved measures, new data collection efforts, or links between existing data sets.

Action 5.A.3: Make needed improvements to data

HHS will address the identified data needs or possible improvements and develop questions to be fielded for data collection. These questions will be added to existing surveys, be part of supplements to existing surveys, or form the basis of a new survey.

Strategy 5.B: Monitor Progress on the National Plan

The National Plan is intended to be a roadmap for accomplishing its five goals. It is a document that is designed to be updated regularly. HHS is committed to tracking progress and incorporating findings into an updated National Plan.

Action 5.B.1: Designate responsibility for action implementation

HHS will designate an office and a contact person responsible and accountable for implementing each action step in the National Plan. The Office of the Assistant Secretary for Planning and Evaluation (ASPE) will be responsible for overseeing implementation, reporting on progress, convening the Advisory Council on Alzheimer's Research, Care, and Services, and issuing reports to Congress.

Action 5.B.2: Track plan progress

HHS will monitor progress to determine whether actions are being completed as stated in the National Plan and the extent to which implemented actions contribute to the desired outcomes and changes associated with each strategy. HHS and its federal partners will identify challenges to the successful completion of strategies and actions and make recommendations for how they can be addressed. For each *strategy*, HHS will monitor available population-based data, such as the National Health and Aging Trends Study, Medicare Current Beneficiary Survey, or the Behavioral Risk Factor Surveillance System to assess the extent to which progress is being made. HHS will use data from both the public and private sectors, as appropriate, to track progress on the National Plan. Additionally, HHS will work to incorporate measures related to AD into other surveillance efforts to monitor population health, such as Healthy People 2020 which, for the first time incorporates objectives related to AD.

For each *action*, HHS will track implementation to determine whether actions are completed in a timely and successful manner. Appendix 4 provides a timeline, method of action, and identifies lead and partner agencies for each action step in the plan. Progress on each of these actions will be reported biannually to the Advisory Council.

Action 5.B.3: Update the National Plan annually

Tracking progress will help HHS and the Advisory Council monitor progress towards the goals of the National Plan and make recommendations for priority actions and updates to the Plan. HHS will incorporate its findings and the recommendations of the Advisory Council to update the National Plan on an annual basis.

Appendix 1: List of Participating Departments and Agencies

ACF -- Administration for Children and Families

ADD -- Administration on Developmental Disabilities

AoA -- Administration on Aging

AHRQ -- Agency for Healthcare Research and Quality

ASPA -- Assistant Secretary for Public Affairs

ASPE -- Assistant Secretary for Planning and Evaluation

CDC -- Centers for Disease Control and Prevention

CMMI -- Center for Medicare and Medicaid Innovation

CMS -- Centers for Medicare and Medicaid Services

DoD -- Department of Defense

FDA -- Food and Drug Administration

HHS -- Department of Health and Human Services

HRSA -- Health Resources and Services Administration

HUD -- Department of Housing and Urban Development

IHS -- Indian Health Service

NIA -- National Institute on Aging

NIH -- National Institutes of Health

NSF -- National Science Foundation

OASH -- Office of the Assistant Secretary for Health

OD -- Office on Disability

ONC -- Office of the National Coordinator of Health Information Technology

OSG -- Office of the Surgeon General

SAMHSA -- Substance Abuse and Mental Health Services Administration

VA -- Department of Veterans Affairs

Appendix 2: Crosswalk: National Plan to Address Alzheimer’s Disease Goals and Objectives, and Related Strategies

National Alzheimer’s Plan (2012)	Multiple Chronic Conditions: A Strategic Framework (2010)	HHS Action Plan to Reduce Racial and Ethnic Health Disparities (2011)	National Prevention Strategy (2011)	HHS Strategic Plan (2010-2015)
Research				
<p>Goal 1: Prevent and Effectively Treat Alzheimer’s Disease by 2025</p> <p>Strategy 1.A: Identify research priorities and milestones</p> <p>Strategy 1.B: Expand research aimed at preventing and treating Alzheimer’s disease</p> <p>Strategy 1.C: Accelerate efforts to identify early and presymptomatic stages of Alzheimer’s disease</p> <p>Strategy 1.D: Coordinate research with international public and private entities</p> <p>Strategy 1.E: Facilitate translation of findings into medical practice and public health programs</p>	<p>Goal 4: Facilitate research to fill knowledge gaps about, and interventions and systems to benefit, individuals with multiple chronic conditions.</p> <p>Objective A: Increase the external validity of trials</p> <p>Objective B: Understand the epidemiology of multiple chronic conditions</p> <p>Objective C: Increase clinical, community, and patient-centered health research</p> <p>Objective D: Address disparities in multiple chronic conditions populations</p>		<p>Strategic Direction 4 -- Elimination of Health Disparities</p> <p>4.4 -- Support research to identify effective strategies to eliminate health disparities</p>	<p>Goal 2: Advance Scientific Knowledge and Innovation</p> <p>Objective A: Accelerate the process of scientific discovery to improve patient care</p> <p>Objective B: Foster innovation to create shared solutions</p> <p>Objective D: Increase our understanding of what works in public health and human service practice</p>

National Alzheimer's Plan (2012)	Multiple Chronic Conditions: A Strategic Framework (2010)	HHS Action Plan to Reduce Racial and Ethnic Health Disparities (2011)	National Prevention Strategy (2011)	HHS Strategic Plan (2010-2015)
Quality Workforce and Evidence-based Strategies				
<p>Goal 2: Enhance Care Quality and Efficiency</p> <p>Strategy 2.A: Build a workforce with the skills to provide high-quality care</p> <p>Strategy 2.B: Ensure timely and accurate diagnosis</p> <p>Strategy 2.C: Educate and support people with AD and their families upon diagnosis</p> <p>Strategy 2.D: Identify high-quality dementia care guidelines and measures across care settings</p> <p>Strategy 2.E: Explore the effectiveness of new models of care for people with AD</p> <p>Strategy 2.F: Ensure that people with AD experience safe and effective transitions between care settings and systems</p> <p>Strategy 2.G: Advance coordinated and integrated health & long-term services and supports for individuals living with AD</p> <p>Strategy 2.H: Improve care for populations disproportionately affected by AD and for populations facing care challenges</p>	<p>Goal 1: Foster health care and public health system changes to improve the health of individuals with multiple chronic conditions.</p> <p>Objective A: Identify evidence-supported models for persons with multiple chronic conditions to improve care coordination</p> <p>Goal 3: Provide better tools and information to health care, public health, and social services workers who deliver care to individuals with multiple chronic conditions.</p> <p>Objective A: Identify best practices and tools</p> <p>Objective B: Enhance health professionals training</p> <p>Objective C: Address multiple chronic conditions in guidelines</p>	<p>Goal 2: Strengthen the Nation's Health and Human Services Infrastructure and Workforce</p> <p>Strategy 2.A: Increase the ability of all health professions and the health care system to identify and address racial and ethnic disparities</p> <p>Goal 3: Advance the health, safety, and well-being of the American people</p> <p>Strategy 3.A: Reduce disparities in population health by increasing the availability and effectiveness of community-based programs and policies</p>	<p>Strategic Direction 4 -- Elimination of Health Disparities</p> <p>4.2 -- Reduce disparities in access to quality health care</p> <p>4.3 -- Increase the capacity of the prevention workforce to identify and address disparities</p>	<p>Goal 2: Advance Scientific Knowledge and Innovation</p> <p>Objective D: Increase our understanding of what works in public health and human service practice</p> <p>Goal 3: Advance the Health, Safety, and Well-Being of the American People</p> <p>Objective C: Improve the accessibility and quality of supportive services for people with disabilities and older adults</p> <p>Goal 5: Strengthen the National Health and Human Service Infrastructure and Workforce</p> <p>Objective B: Ensure that the Nation's health care workforce can meet increased demands</p> <p>Objective C: Enhance the ability of the public health workforce to improve public health at home and abroad</p> <p>Objective D: Strengthen the Nation's human service workforce</p>

National Alzheimer's Plan (2012)	Multiple Chronic Conditions: A Strategic Framework (2010)	HHS Action Plan to Reduce Racial and Ethnic Health Disparities (2011)	National Prevention Strategy (2011)	HHS Strategic Plan (2010-2015)
Individual and Family Supports				
<p>Goal 3: Expand Supports for People with AD and Their Families</p> <p>Strategy 3.A: Ensure receipt of culturally sensitive education, training, and support materials</p> <p>Strategy 3.B: Enable family caregivers to continue to provide care while maintaining their own health and well-being</p> <p>Strategy 3.C: Assist families in planning for future care needs</p> <p>Strategy 3.D: Maintain the dignity, safety and rights of people with Alzheimer's disease</p> <p>Strategy 3.E: Assess and address housing needs of people with AD</p>	<p>Goal 2: Maximize the use of proven self-care management and other services by individuals with multiple chronic conditions.</p> <p>Objective B: Facilitate home and community-based services.</p>	<p>Goal 1: Transform Health Care</p> <p>Strategy 1.A: Reduce disparities in health insurance coverage and access to care</p> <p>Strategy 1.B: Reduce disparities in access to primary care services and care coordination</p> <p>Strategy 1.C: Reduce disparities in the quality of health care</p>	<p>Strategic Direction 2 -- Clinical and Community Preventive Services</p> <p>2.4 -- Support implementation of community-based preventive services and enhance linkages with clinical care</p> <p>2.5 -- Reduce barriers to accessing clinical community preventive services, especially among populations at greatest risk</p> <p>Strategic Direction 1 -- Healthy and Safe Community Environments</p> <p>1 -- Coordinate investments in transportation, housing, environmental protection, and community infrastructure to promote sustainable and healthy communities</p>	<p>Goal 3: Advance the Health, Safety, and Well-Being of the American People</p> <p>Objective C: Improve the accessibility and quality of supportive services for people with disabilities and older adults</p> <p>Goal 1: Transform Health Care</p> <p>Objective B: Improve health care quality and patient safety</p> <p>Objective C: Emphasize primary & preventive care linked with community prevention services</p>

National Alzheimer's Plan (2012)	Multiple Chronic Conditions: A Strategic Framework (2010)	HHS Action Plan to Reduce Racial and Ethnic Health Disparities (2011)	National Prevention Strategy (2011)	HHS Strategic Plan (2010-2015)
Informed Stakeholders				
<p>Goal 4: Enhance Public Awareness and Engagement</p> <p>Strategy 4.A: Educate the public about Alzheimer's disease</p> <p>Strategy 4.B: Work with state and local governments to improve coordination and identify model initiatives to advance Alzheimer's disease awareness and readiness across the government</p>			<p>Strategic Direction 3 -- Empowered People</p> <p>3.3 -- Engage and empower people and communities to plan and implement prevention policies and programs</p> <p>Priority 7 -- Mental and Emotional Well-being</p> <p>7.3 -- Provide individuals and families with the support necessary to maintain positive mental well-being</p>	
Quality Data				
<p>Goal 5: Improve Data to Track Progress</p> <p>Strategy 5.A: Enhance the federal government's ability to track progress</p> <p>Strategy 5.B: Monitor progress on the National Plan</p>		<p>Goal 4: Advance Scientific Knowledge and Innovation</p> <p>Strategy 4.A: Increase the availability and quality of data collected and reported on racial and ethnic minority populations</p>		<p>Goal 4: Increase Efficiency, Transparency, and Accountability of HHS Programs</p> <p>Objective C: Use HHS data to improve the health and well-being of the American people</p>

Appendix 3: Inventory of Federal Alzheimer’s Disease Research, Clinical Care, and Long-Term Services and Supports Programs (FY2010)

Purpose and Scope

The National Alzheimer’s Project Act (NAPA), enacted in 2011, requires the Secretary of the U.S. Department of Health and Human Services (HHS) to establish a national plan to address Alzheimer’s disease. NAPA requires coordination of Alzheimer’s research and services across all federal agencies and an annual assessment of the nation’s progress in preparing for the escalating burden of Alzheimer’s disease. One of the requirements of NAPA is an initial evaluation of all federally funded efforts in Alzheimer’s research, clinical care, and institutional, home, and community-based programs.

Shortly after the legislation was passed, the Secretary of HHS established a Federal Interagency Group on Alzheimer’s Disease and Related Dementias to develop an inventory of federal programs related to Alzheimer’s disease. The interagency group created this inventory of federally-funded efforts in three broad categories: research, long-term services and supports, and clinical care. Representatives from various federal agencies reviewed the portfolios of programs administered by their agencies and identified those related to Alzheimer’s disease in Fiscal Year 2010, the most recent year for which complete data were available. This appendix provides a summary of those federally-funded programs.

Seven agencies within HHS -- the Administration on Aging, the Agency for Healthcare Research and Quality, the Centers for Medicare and Medicaid Services, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the National Institutes of Health, and the Substance Abuse and Mental Health Services Administration -- as well as the U.S. Department of Defense, the U.S. Department of Justice, and the U.S. Department of Veterans Affairs -- identified Alzheimer’s disease-relevant programs. For FY2010, these agencies reported a combined total of 1,428 programs and projects, across 14 categories of research, clinical care, and long-term services and supports that address Alzheimer’s disease. However, this is only a subset of the federal activities that support people with Alzheimer’s disease and their caregivers. Because people with Alzheimer’s disease or their caregivers are covered by broader programs and data limitations make it difficult to specifically identify these individuals and the services they receive, the Alzheimer’s disease component of many federal programs could not be determined.

Consistent with the approach in the NAPA legislation and National Plan, the term “Alzheimer’s disease” refers to Alzheimer’s disease and related dementias. Related dementias include frontotemporal, Lewy body, mixed, and vascular dementia. It is often difficult to distinguish between Alzheimer’s disease and other dementias. Some of the basic neurodegenerative processes of these diseases have common pathways. People with dementia and their families face similar challenges in finding appropriate and necessary medical and supportive care. Unless otherwise noted, in this inventory Alzheimer’s disease refers to these conditions collectively.

Methodology for the Inventory

Federal departments, including HHS, the Department of Defense, the Department of Justice, and the Department of Veterans Affairs, used the following search terms to identify projects that they supported during FY2010: Alzheimer’s disease, dementia, mild cognitive impairment, and frontotemporal dementias. Representatives from each agency then sorted the projects they identified into the categories below, as defined by federal interagency subgroups on research, clinical care, and long-term services and support programs:

Research Subgroup

- Molecular pathogenesis and physiology
- Diagnosis, assessment, and disease monitoring
- Translational research and clinical interventions
- Epidemiology
- Care, support, and health economics
- Research resources

Clinical Care Subgroup

- Detection and diagnosis
- Clinical management and care coordination

Long-Term Services and Supports Subgroup

- Home and community-based services
- Residential care settings
- Quality and safety
- Planning for future care needs

In the report below, programs and initiatives are organized by these categories. In the Supplementary Material section at the end of the document, this material is presented in tabular form and organized by agency.

Research

Federally funded research on Alzheimer's disease includes a broad range of activities: basic and epidemiologic research, development of non-pharmacologic and pharmacologic treatments and interventions, clinical testing of the efficacy and safety of interventions, and development and implementation of regulatory processes across the research continuum.

The FY 2010 Federal Inventory for research will be available in more detail and updated annually at <http://www.nia.nih.gov/research/dn/international-alzheimers-disease-research-portfolio>.

Several of the grant mechanisms supported by Federal agencies are used to promote multidisciplinary and collaborative research.

Molecular Pathogenesis and Physiology of Alzheimer's Disease

The overarching aim of the research within this category is to identify and understand the molecular, cellular and physiological mechanisms that cause Alzheimer's disease. The spectrum of research under this category includes studies on the genes that affect the risk for AD; molecular and cellular factors that may contribute to AD; and lifestyle risk factors. In addition, research under this category focuses on what makes nerve cells lose function and die, leading to loss of memory and eventually dementia. Findings from these studies are important in identifying potential targets for the prevention, diagnosis, and treatment of Alzheimer's disease. Basic research includes developing and first-line testing of new preventive and therapeutic compounds for Alzheimer's in preclinical models.

Diagnosis, Assessment, and Disease Monitoring

Finding a reliable way to detect Alzheimer's disease early in its development is critical to devising future treatments that may delay, prevent, or treat the disease. Studies show that changes in the brain caused by Alzheimer's disease may begin to develop years, even decades, before clinical symptoms become apparent. Researchers are developing blood and cerebrospinal fluid biomarkers, clinical assessments, and brain imaging technologies to diagnose AD as early as possible. Studies measuring changes in the structure and function of the brain and biomarkers measures may provide clues to pre-symptomatic AD and will allow researchers to gauge more efficiently the effectiveness of interventions in clinical trials. Once validated, these measures will also allow for the assessment of disease risk and cognitive function.

Translational Research and Clinical Interventions

Translational research brings knowledge from the laboratory and develops into new interventions that can be tested in clinical trials. Such research can then lead to the development of safe and effective interventions for Alzheimer's disease and mild cognitive impairment, often the first stage in the development of dementia. Clinical trials are now underway to test promising new drugs, behavioral interventions such as exercise, or a combination of interventions with the intention of moving successful interventions rapidly into clinical practice. Researchers are also testing the possible repurposing and reformulation of existing drugs already approved for other diseases and conditions and the development of other therapeutics. Much of this work involves innovative collaborations among scientists who focus on understanding the cellular, molecular, and pathologic dimensions of Alzheimer's disease and clinicians who focus on treating people with the disease.

Epidemiology

Epidemiological and longitudinal studies focus on understanding the scope and dimensions of Alzheimer's disease at the population level. They can help us identify initial clues to risk and protective factors that may be associated with disease development as well as specific populations that may be at increased risk. Researchers who conduct epidemiologic studies develop and test measures to track trends in prevalence and incidence, including trends among subpopulations, and correlate these trends with changes in environmental and biological factors. Understanding the scope and reach of cognitive impairment and Alzheimer's disease has important implications, including better understanding of the increased risk of disability and the need for supportive services for those with the disease and those who care for them.

Care, Support and Health Economics of Alzheimer's Disease

Research in this category includes projects that are developing interventions and strategies for improving quality of care for people with Alzheimer's disease (AD) across diverse populations in a variety of care settings. This category also addresses the unique needs of not only people with AD, but also those of their caregivers. It includes developing effective and culturally appropriate strategies to understand and help alleviate the stress, anxiety, depression and other health consequences often associated with caring intensely for someone with AD. Changes in biomarkers, mental health outcomes, and health behaviors are investigated as indicators of caregiving burden. In addition, this category includes research investigating the direct and indirect costs for the care of both the person with the disease and caregivers (both professional and unpaid).

Research Resources

The research infrastructure enables high quality research across the entire continuum of research from basic science to development of therapies, clinical research and community health care. Funded resources include research centers that provide clinical, data management, administrative, educational and technological support to AD researchers. In addition, funded resources include data and tissue repositories such as brain banks and professional and career development training. These resources provide researchers with access to the technology and equipment they need to perform research at the highest levels and ensure the availability of a skilled, motivated, multidisciplinary work force. These activities also include workshops, symposia, and conferences to facilitate the dissemination of research findings to the scientific and health professional communities and to the public.

Four agencies -- the National Institutes of Health, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, and Department of Veterans Affairs -- identified relevant research in the six research categories. For FY2010, these agencies reported a combined total of 1,393 projects. Exhibit 1 provides numbers of projects across the six research categories for each of the four agencies. The Food and Drug Administration (FDA) and National Science Foundation (NSF) support research that may also have implications for, but are not specifically focused on, Alzheimer's disease.

EXHIBIT 1. Number of Projects across Research Categories of Alzheimer's Disease and Other Related Dementias by Federal Agency, FY 2010						
Federal Agency	Molecular Pathogenesis & Physiology	Diagnosis, Assessment & Disease Monitoring	Translational Research & Clinical Interventions	Epidemiology	Care, Support & Health Economics	Research Resources
National Institutes of Health/HHS	578	233	120	75	23	228
Centers for Disease Control and Prevention/HHS	—	—	—	5	—	—
Agency for Healthcare Research and Quality/HHS	—	1	1	2	10	1
Department of Veterans Affairs	44	22	16	10	19	—
Total	622	256	137	92	52	229
Total Number of Projects: 1,393						

Clinical Care

Clinical services encompass a broad range of medical, nursing, and other associated health services that are needed to, detect, diagnose, and manage Alzheimer's disease. It includes services across the care continuum such as ambulatory care, geriatric primary care, hospice, and across all stages of the disease. Medicare and Medicaid are the primary governmental payers for these services for those with AD who are aged 65 and over, as well as those who meet the categorical eligibility requirements for being considered disabled by these programs. In addition, the Department of Veterans Affairs provides health care for eligible Veterans, including those with AD.

While none of its services are dementia specific, Medicare covers health, acute, and post-acute medical care for people aged 65 and older and for younger populations who meet the Social Security definition of disability. Medicare covers most, but not all, of the cost of inpatient hospital care, doctor's fees, and other medical expenses of people with Alzheimer's disease. Among other services, Medicare covers hospital care, limited skilled nursing facility care, medically-related home health care, outpatient services, durable medical equipment, and prescription drugs. Medicare Part D covers prescription drugs and is available to all Medicare beneficiaries through private insurance plans. All Medicare drug plans cover some medications commonly prescribed to treat Alzheimer's disease. All plans are required to cover at least two cholinesterase inhibitors and memantine. Medicare beneficiaries with a terminal illness, who are certified by a physician to have 6 months or less to live, are eligible for the Medicare hospice benefit. The Medicare hospice benefit includes nursing care, therapies, home health, medical supplies, respite care, bereavement care and other services.

Medicaid also finances clinical services for some people with Alzheimer's disease. Most Medicaid beneficiaries who have Alzheimer's disease are also eligible for Medicare. In situations of dual eligibility, the role of Medicaid (not including Medicaid's important role in covering non-clinical long-term service and support needs) is primarily to pay the Medicare premiums, deductibles, and coinsurance and to cover some acute care services not covered by Medicare. For the relatively few Medicaid beneficiaries with Alzheimer's disease who are not also eligible for Medicare, Medicaid covers a comprehensive range of acute care services. No Medicaid service is dementia specific.

VA provides eligible Veterans with outpatient and inpatient acute care and extended care services. VA's Geriatric Evaluation and Management program provides assessment and care by interdisciplinary teams in inpatient and outpatient settings for older Veterans with multiple medical, functional, and psychosocial problems and geriatric syndromes (e.g., falls). Geriatric evaluation -- the assessment and care plan development -- is required to be provided to all eligible Veterans who may benefit from it.

The programs that Medicare and Medicaid, the VA, the Substance Abuse Mental Health Services Administration (SAMHSA), the Health Resources and Services Administration (HRSA) identified fall into three categories of clinical care: (1) Detection and diagnosis, (2) clinical management and care coordination, and (3) person and family centered goal setting.

Detection and Diagnosis

Clinical diagnosis of dementia often begins with the recognition of a progressive decline in memory; a decrease in the person's ability to perform activities of daily living; or psychiatric problems, personality changes, or problem behaviors. Because persons with Alzheimer's disease may use multiple care settings, providers in all settings need to have the skills to detect possible Alzheimer's disease and to refer a patient for differential diagnosis when necessary.

Clinical Management and Care Coordination

Clinical management of Alzheimer's disease includes drug and non-drug services which may help with both cognitive and behavioral symptoms of the disease. A high percentage of persons with Alzheimer's disease have coexisting chronic medical conditions, the effective management of which involves coordination of care across health care settings.

Health Resources and Services Administration and Centers for Medicare and Medicaid Services

HRSA and CMS have been collaborating to reduce adverse drug events. They formed the Patient Safety and Clinical Pharmacy Services Collaborative (PSPC) to improve the quality of health care by integrating evidence-based clinical pharmacy services into the care and management of high-risk, high-cost, complex patients. The PSPC collaborative includes a joint effort focusing on the Medicare population often at higher risk secondary to polypharmacy or potentially inappropriate medication prescription and use. In addition, the Quality Improvement Organizations (QIOs), run by CMS, will foster reduction of adverse drug events in high-risk populations by expanding community teams focused on people with AD who are at high medication risk because of multiple medications, multiple providers, multiple conditions, or inappropriate or inadequate medication use.

Department of Veterans Affairs

At VA facilities, the majority of ongoing primary care for Veterans, including Veterans with dementia, is provided through a patient-centered, primary care provider-directed, multidisciplinary "Patient-Aligned Care Team (PACT)." Geriatric Primary Care is available for frail elderly Veterans with complex medical histories whose need for in-depth attention, often including management of dementia, may not be adequately addressed in general PACT clinics. Inpatient diagnostic and treatment services include a wide range of specialty care (e.g., geriatrics, neurology, mental health, surgery, and other medical specialties). Home-based Primary Care provides comprehensive, longitudinal, primary care by an interdisciplinary team of VA staff in the homes of Veterans with complex, chronic, disabling disease for whom routine clinic-based care is not effective. When appropriate, home hospice care is provided by community hospice agencies and includes comfort-oriented and supportive services in the home for Veterans in the advanced stages of Alzheimer's disease and other diseases. Some VA facilities have developed specialized dementia or other geriatric problem-focused specialty outpatient clinics, which may provide evaluation or ongoing care.

Substance Abuse and Mental Health Services Administration (SAMHSA)

The Substance Abuse and Mental Health Services Administration (SAMHSA) is implementing an Older Adult Targeted Capacity Expansion (TCE) program. This program is designed to improve consumers' overall mental health and quality of life. Older Adult TCE helps communities provide direct services and build infrastructure to support expanded services for the behavioral health needs of clients from a variety of ethnic and cultural groups. The program provides direct clinical treatment, long-term services and supports, and prevention services. Additionally, it provides "wraparound" and recovery support services (e.g., community integration and transportation services). SAMHSA also maintains the National Registry of Effective Programs and Practices (NREPP), a searchable online registry of more than 190 evidence-based interventions supporting mental health promotion, substance abuse prevention, and mental health and substance abuse treatment. Its purpose is to connect members of the public with intervention developers to learn how to implement these interventions in their communities.

Long-Term Services and Supports

Long-term services and supports help people with Alzheimer's disease with everyday tasks such as eating, bathing, and getting dressed and, in so doing, provide support for their informal caregivers. These services and supports include a broad range of supportive services that may be provided in the home and community, such as home care and adult day care programs, or in residential settings, such as nursing homes, assisted living facilities, or board and care homes. Long-term services and supports generally do not include clinical services that are needed to manage the underlying health conditions of people with disabilities, except when expressly included in a Home and Community-Based Services waiver. The

standard Medicaid and VA benefits packages provide a range of long-term services and supports to people who meet certain eligibility criteria.

Medicaid

CMS provides long-term services and supports to people who meet specific eligibility criteria. These programs cover care in multiple categories of long-term services and supports.

Funded by the CMS, the states, and some counties, Medicaid is the main source of public funding for long-term services and supports and provides coverage for nursing homes and a wide range of home and community-based services. Eligibility is limited to people who have lower incomes or who have functional limitations. In 2009, 34 percent of Medicaid expenditures for long-term services and supports for older people and persons with physical disabilities were for home and community-based services.³⁶

Programs for Veterans

VA provides a range of health care services and supports for eligible Veterans, including those with dementia. Services include in-home, community-based, outpatient and inpatient acute care and extended care services. In general, individuals who served in the active military, naval, or air service and were discharged under any condition other than dishonorable may qualify for VA health care benefits. Once enrolled for VA health care, each Veteran is assigned to a particular priority group, based on criteria such as degree of service-connected disability, income level, and other specific circumstances. There are no separate eligibility criteria for dementia. Services for eligible, enrolled Veterans with dementia are provided throughout the full range of VA health care services.

VA provides a standard health care benefits package for all enrolled Veterans that includes home and community-based services such as home-based primary care, adult day health care, homemaker/home health aide, skilled home care, and respite. These services are provided in the community under a system of case management provided by VA staff. Home-based primary care includes caregiver education and support. Adult day health care is provided in VA settings and purchased from community providers. Purchased skilled home care are services provided to Veterans who are homebound and in need of skilled services such as nursing, physical, occupational, and speech therapy, or social services. In-home or institutional respite care can be arranged to temporarily relieve the spouse or other caregiver from the burden of caring for a chronically ill or disabled Veteran at home.

Most programs that provide long-term services and supports include but do not target people with Alzheimer's disease exclusively. Two agencies -- the Administration on Aging and the Department of Justice -- identified home and community-based services that exclusively focus on people with Alzheimer's disease.

Administration on Aging

The Administration on Aging administers the Alzheimer's Disease Supportive Services Program. This state-based grant program supports efforts to expand the availability of community-level supportive services for persons with Alzheimer's and their caregivers and improve the responsiveness of the home and community-based care system to persons with dementia. Support provided includes translation of evidence-based interventions into effective supportive service programs at the community level. The availability of services may be statewide or concentrated in targeted communities.

The Administration on Aging also administers the National Alzheimer's Call Center. The Call Center provides national information and counseling services for persons with Alzheimer's disease, their family members, and unpaid caregivers. The Call Center is available nationally and operates 24 hours a day, 7 days a week, 365 days a year. The Call Center provides expert advice, care consultation, information, and referrals nationwide.

Department of Justice

In FY2010, the Department of Justice operated the Missing Alzheimer's Disease Patient Alert Program. This community-based program supports state and local projects that aid in the protection and location of missing persons with Alzheimer's disease and related dementias and other missing elderly individuals.

Three agencies, the Administration on Aging, Centers for Medicare & Medicaid Services, and Department of Veterans Affairs, identified relevant long-term services and supports in their portfolios. Most AoA and CMS programs include a state-federal partnership with participation requiring matching funding from the states. These programs fell into four categories: (1) services in residential care settings, (2) home and community-based services, (3) quality and safety, and (4) planning for long-term services and supports.

Services in Residential Care Settings

Some long-term services and supports are provided in settings other than the home of the person with Alzheimer's disease or the family caregiver including skilled nursing facilities (nursing homes) and residential care facilities, such as assisted living and board and care homes. More than 50 percent of residents in assisted living and nursing homes have some form of dementia or cognitive impairment.³⁷

Centers for Medicare and Medicaid Services

All states are required to cover nursing home care as part of their Medicaid programs. In 2009, 64 percent of Medicaid expenditures for long-term services and supports for older people and persons with physical disabilities were for nursing home care.³⁸ In addition, state Medicaid programs may cover the service portion of residential care facilities through their home and community-based services waivers; room and board may not be covered. In 2009, 37 states covered residential care services through their home and community-based services waivers.³⁹ State Medicaid programs may also provide coverage for personal care services in residential care facilities through their state-plan personal care option; in 2009, 13 states used this mechanism to finance services. Some states use more than one approach.

Department of Veterans Affairs

VA participates in three nursing home programs, each of which has unique eligibility and admission criteria. One is the VA-operated Community Living Center (CLC) program (formerly known as VA Nursing Home Care Units). VA CLCs, which are located on or near VA Medical Center campuses, provide a dynamic array of short and long stay services. Services include skilled nursing, rehabilitation, mental health recovery, spinal cord injury care, dementia care, and respite care, among others. Some VA CLCs have established separate dementia units, a physically secure section used exclusively to care for Veterans with dementia. VA also contracts for care of Veterans in community nursing homes approved by VA, with VA staff providing quality oversight. The Community Nursing Home program has the advantage of being offered in many local communities where Veterans can receive care near their homes and families. The State Veterans Home Program is a grant program where a state petitions VA for a portion of the facility construction costs and a per diem for each Veteran served. The state and the Veteran also contribute to the Veteran's care costs. State Veterans Homes are operated by the states, which set specific admission criteria. For example, State Veterans Homes may admit non-Veteran spouses. VA surveys State Veterans Homes for compliance with VA standards.

VA also participates in two residential care programs. One is Community Residential Care, which provides room, board, limited personal care, and supervision to Veterans who do not require hospital or nursing home care but are not able to live independently because of medical or psychiatric conditions, and who have no family to provide care. The Veteran pays for the cost of this living arrangement, and VA provides inspection of the home and periodic visits by VA health care professionals. Some VA Medical Centers offer a new version of this program, called Medical Foster Home, in which the Veteran lives in a Community Residential Care home and is enrolled in VA Home-Based Primary Care.

Home and Community-Based Services

Home and community-based services include a wide range of services, including personal care, adult day care, homemaker services, home-delivered meals, respite care, caregiver supports and education, and various assistive technologies.

Centers for Medicare and Medicaid Services

Medicaid home and community-based services waivers (authorized by Section 1915(c) of the Social Security Act) permit state Medicaid programs to offer a wide range of home and community-based services to individuals who require an institutional level of care, including nursing facility care, and meet certain income and asset eligibility tests. Services covered by the waiver may include a wide range of long-term services and supports. Forty-seven states operate 1915(c) Home and Community-Based waivers; one other state covers a similar set of services through a statewide research and demonstration waiver.

States may also cover personal care as a Medicaid optional service. Personal care includes help with daily activities such as eating, bathing, and dressing. Medicaid beneficiaries who are eligible for the personal care state option must have a disability, but are not required to need an institutional level of care. States may not limit the number of people receiving personal care services, and there is no federal expenditure limit.

States can also offer a variety of services under the Section 1915(i) State Plan Home and Community-Based Services (HCBS) benefit. A handful of states have adopted the 1915(i) option. This Medicaid state plan option is similar to Medicaid home and community-based services waivers, but this option does not require individuals to need an institutional level of care. In addition, CMS's Money Follows the Person program transitions people living in nursing homes and other institutions to homes, apartments, or group homes in the community. Approximately 24 states provide transitional services to individuals who have Alzheimer's.

Administration on Aging

The Administration on Aging identified two programs that serve caregivers of persons with Alzheimer's disease. The National Family Caregiver Support Program funds a range of supports nationwide that assist family and informal caregivers to care for their loved ones at home. The program supports five services: information to caregivers about available services; assistance to caregivers in gaining access to the services; individual counseling, organization of support groups, and caregiver training; respite care; and supplemental services. Services are provided by local community organizations. The Lifespan Respite Care Program helps to support, expand, and streamline the delivery of planned and emergency respite services for caregivers of people with disabilities of all ages. This program also supports the recruitment and training of respite workers and caregiver training and empowerment. Services supported by this program are available in certain localities.

Department of Veterans Affairs

VA provides home-based primary care, adult day health care, homemaker or home health aides, skilled home care, respite, and home hospice care to eligible Veterans. VA social workers assist caregivers with accessing support services such as respite care, adult day health services, in-home aide services, and support groups. VA also has a toll-free Caregiver Support Line staffed by licensed social workers (1-855-260-3274). The Support Line can link Veterans or their family caregivers to their local VA medical center to receive services.

Quality and Safety Programs

Quality and safety programs aim to improve the quality of care and quality of life of people receiving services and help ensure that individuals are safe. This category includes all programs aimed at reducing neglect and abuse of persons with Alzheimer's disease who are especially vulnerable to those who might take advantage of their cognitive impairment, and also includes programs which ensure the delivery of quality care. Ensuring quality and safety is addressed, in part, by appropriate assurance systems, including regulatory oversight by federal and state agencies.

Administration on Aging

Both the Administration on Aging's Prevention of Elder Abuse, Neglect and Exploitation Program and the Long-Term Care Ombudsman Program aim to reduce neglect and abuse of persons with Alzheimer's disease and other people with disabilities. The Elder Abuse, Neglect and Exploitation Program strengthens state-based elder justice strategic planning and direction for programs, activities, and research related to elder abuse awareness and prevention. In addition, the program funds training for law enforcement officers, health care providers, and other professionals on how to recognize and respond to elder abuse; supports outreach and education campaigns to increase public awareness of elder abuse and how to prevent it; and supports the efforts of elder abuse prevention coalitions and multidisciplinary teams.

The Long-Term Care Ombudsman program provides nationwide support for advocates for residents of nursing homes, board and care homes, assisted living facilities, and similar adult care facilities. The ombudsmen actively resolve problems of individual residents and advocate for changes at the local, state, and national levels that will improve residents' care and quality of life.

Centers for Medicare and Medicaid Services

CMS, in cooperation with the states, has extensive mechanisms to monitor quality in nursing homes and in home health. Nursing homes cannot operate unless they are licensed by the state in which they are located, and they cannot receive Medicare and Medicaid funding unless they are certified as meeting federal quality standards. CMS maintains oversight for compliance with the federal health and safety standards for nursing homes serving Medicare and Medicaid beneficiaries. State Survey Agencies carry out the certification process. To monitor state compliance with federal rules, CMS performs comparative surveys to gauge the performance of the state survey system. A similar process operates for home health agencies. States, rather than the federal government, regulate residential care facilities and non-skilled home care agencies.

Planning for Future Care Needs

Preparing to access long-term services and supports requires planning ahead. For individuals without a diagnosis of Alzheimer's disease, this may include planning for a potential need for long-term services and supports, as part of retirement planning, through personal savings, long-term care insurance or legal documentation. For families who have a loved one with a new diagnosis, planning may include using case management services to learn about what service options are available to determine which will best meet their needs. Individuals, families, and supportive service systems benefit from established plans of care for health and long-term services and supports.

Administration on Aging

The Administration on Aging identified several relevant programs. Case management services are available through the Area Agencies on Aging nationwide to assist in assessing needs, developing care plans, and arranging services for older persons or their caregivers. Aging and Disability Resource Center networks serve as sources of information on the range of long-term services and support options for persons regardless of age, income, or disability with one-on-one help in understanding and accessing services and supports. In addition, Legal Assistance Programs protect older persons from direct challenges to independence, choice, and financial security. These programs, available nationwide, help older individuals understand their rights, exercise options through informed decision-making, and achieve optimal benefit from the support and opportunities promised by law.

Appendix 4: Implementation Milestones

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
JANUARY - JUNE, 2012				
5.B.1	Designate responsibility for action implementation	Create and regularly update a National Plan implementation monitoring tool	ASPE	Completed
1.A.2	Solicit public and private input regarding Alzheimer's disease	Request for Information (RFI) inviting public and private input on funded research addressing Alzheimer's disease and related dementias	NIH/NIA	Completed
1.D.1	Inventory Alzheimer's disease research investments	Compile portfolios of domestic and international funders of AD research and make the information available to public through searchable online database	NIH/NIA	May 2012
1.D.2	Expand international outreach to enhance collaboration	Invite international colleagues to meet and discuss AD research priorities and collaboration	NIH/NIA	May 2012
5.B.2	Track plan progress	Track progress on the plan, and incorporate measures into other efforts to monitor population health such as Healthy People 2020	ASPE	May 2012
1.A.1	Hold an international Alzheimer's disease research summit to identify priorities, milestones, and a timeline	Convene Alzheimer's Research Summit 2012: Path to Treatment and Prevention: Meeting	NIH/NIA (National and international experts, public and private stakeholders, members of the Advisory Council on Alzheimer's Research, Care, and Services)	May 2012
1.B.3	Increase enrollment in clinical trials and other clinical research through community, national, and international outreach	Organize meetings to identify approaches and coordination points for these efforts	FDA, NIH/NIA (VA, CDC, ADD, HRSA, AoA)	June 2012
2.A.5	Strengthen the state aging and public health workforce	Coordinate with states to develop workforces that are AD-capable and culturally competent, include enhancing Alzheimer's disease competencies among Aging Network staff	AoA, CDC	June 2012
2.B.2	Identify and disseminate appropriate assessment tools	Identify appropriate assessment tools that can be used in a variety of outpatient settings, including the Medicare Annual Wellness Visit, to assess cognition. Disseminate recommended tools to practitioners.	CMS, NIH/NIA (CDC)	June 2012

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
2.F.2	Implement and evaluate new care models to support effective care transitions for people with AD	Award grants for Community-based Care Transition Program demonstration grants	CMS (AoA)	June 2012
3.B.6	Share lessons learned through VA caregiver support strategies with federal partners	Hold scheduled informational meetings	VA (Federal partners)	June 2012
3.C.2	Expand long-term care awareness efforts	Develop campaign materials	AoA	June 2012
JULY - DECEMBER, 2012				
2.A.2	Encourage providers to pursue careers in geriatric specialties	Enhance (1) the Comprehensive Geriatric Education Program, (2) the Geriatric Academic Career Awards Program; and (3) training projects that provide fellowships for individuals studying to be geriatricians, geriatric dentists, or geriatric psychiatrists	HRSA	July 2012
2.A.4	Strengthen the direct-care workforce	Release training for the nursing home direct care workforce	CMS (AHRQ)	July 2012
2.A.3	Collect and disseminate dementia-specific guidelines and curricula for all provider groups across the care spectrum	Convene meeting with public and private partners	HRSA (VA, CMS, NIH, IHS)	July 2012
2.D.1	Explore programmatically relevant dementia care guidelines and measures	Convene meetings with public and private organizations to discuss programmatically relevant dementia care guidelines and practices	CMS (AHRQ, VA, ASPE, AoA, SAMHSA)	July 2012
4.A.1	Design and conduct a national education and outreach initiative	Design a national education and outreach initiative and implement with states, local governments, and NGOs.	AoA (NIH/NIA, CDC, CMS, HRSA, IHS, SAMHSA, OSG)	July 2012
5.B.2	Track plan progress	Track progress on the plan, and incorporate measures into other efforts to monitor population health such as Healthy People 2020. Agency representatives report out biannually after July 2012	ASPE	July 2012
5.B.2	Track plan progress	Provide summary of data to states that included the BRFSS Cognitive Impairment module	CDC	July 2012
1.B.3	Increase enrollment in clinical trials and other clinical research through community, national, and international outreach	Organize meetings to identify approaches and coordination points for these efforts; implement an action plan that incorporates these ideas.	FDA, NIH/NIA (VA, CDC, ADD, HRSA, AoA)	August 2012

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
1.C.2	Maximize collaboration among federal agencies and with the private sector	Identify additional partnership opportunities with the private sector and facilitate collaborative efforts to enhance identification of risk factors and early biomarkers.	NIH/NIA (FDA, CMS)	August 2012
2.H.1	Create a taskforce to improve care for these specific populations	Convene taskforce	ASPE, ADD (AoA, NIH, OD, NIMH)	August 2012
3.D.1	Educate legal professionals about working with people with Alzheimer's disease	Develop training materials	AoA (NLRC)	August 2012
3.D.1	Educate legal professionals about working with people with Alzheimer's disease	Conduct training webinars	AoA (NLRC)	August 2012
1.A.1	Hold an international Alzheimer's disease research summit to identify priorities, milestones, and a timeline	Release report summarizing the Alzheimer's Research Summit 2012: Path to Treatment and Prevention.	NIH/NIA (National and international experts, public and private stakeholders, members of the Advisory Council on Alzheimer's Research, Care, and Services)	August 2012
1.E.1	Identify ways to compress the time between target identification and release of pharmacological treatments	Examine current average time and identify places where the timeline could be shortened.	ASPE, NIH (FDA,)	September 2012
2.A.6	Support state, tribal, and local Alzheimer's Strategies	Convene meeting with federal government partners, state, tribal, and local officials	AoA (ASPE, CDC, HRSA)	September 2012
2.B.1	Link the public to diagnostic and clinical management services	Convene representatives from National Alzheimer's Call Center and Aging Network to establish inventory of resources available to the public.	AoA, NIH/NIA	September 2012
3.B.3	Review the state of the art of evidence-based interventions that can be delivered by community-based organizations	Identify promising interventions for research, translation, and expansion into practice at the community level	AoA (Private partners, NIH/NIA, CDC)	September 2012
5.A.1	Identify major policy research needs	Convene federal partners to identify current and future policy and research questions; identify gaps in data	ASPE (CMS, CDC, NIH/NIA, AoA, VA, Advisory Council)	September 2012
2.C.1	Educate physicians and other health care providers about accessing long-term services and supports	Convene Federal partners, public and private entities and the provider community to identify information about available resources.	HRSA (CMS, CDC, NIH/NIA, AoA, VA)	October 2012

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
2.G.1	Review evidence on care coordination models for people with AD	Convene meeting to review existing research on care coordination models; ask group to define the health and psychosocial outcomes on which the interventions will be evaluated	ASPE	October 2012
3.D.1	Educate legal professionals about working with people with Alzheimer's disease	Provide summary reports of the training webinars	AoA (NLRC)	October 2012
4.B.1	Convene leaders from state, tribal, and local governments	Convene to identify steps for raising AD awareness and readiness.	OEA, IHS (ASPE, ASPA, AoA, CDC)	October 2012
3.B.6	Share lessons learned through VA caregiver support strategies with federal partners	Scheduled informational meetings	VA (Federal partners)	November 2012
1.B.3	Increase enrollment in clinical trials and other clinical research through community, national, and international outreach	Implement an action plan that incorporates ideas from meeting	FDA, NIH/NIA (VA, CDC, ADD, HRSA, AoA)	December 2012
2.A.3	Collect and disseminate dementia-specific guidelines and curricula for all provider groups across the care spectrum	Develop dementia-specific guidelines and curricula	HRSA (VA, CMS, NIH, HIS)	December 2012
2.A.3	Collect and disseminate dementia-specific guidelines and curricula for all provider groups across the care spectrum	Develop website with appropriate links and contact info	HRSA (VA, CMS, NIH, HIS)	December 2012
2.A.5	Strengthen the state aging and public health workforces	Report on progress annually	AoA, CDC	December 2012
2.B.2	Identify and disseminate appropriate assessment tools	Survey providers who have used the toolbox.	CMS, NIH/NIA (CDC)	December 2012
2.C.2	Enhance assistance for people with AD and their caregivers to prepare for care needs	AoA will develop training materials for Options Counseling which includes best practices for working with persons with cognitive impairments and their caregivers.	AoA	December 2012
2.C.2	Enhance assistance for people with AD and their caregivers to prepare for care needs	Update tools and resources to educate caregivers about available programs and resources	AoA (CDC)	December 2012
2.D.1	Explore programmatically relevant, dementia care guidelines and measures	Identify 3-5 measures within the first year; submit measures and programmatically relevant guidelines to National Quality Forum	CMS (AHRQ, VA, ASPE, AoA)	December 2012

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
2.D.1	Explore programmatically relevant, dementia care guidelines and measures	Identify 3-5 measures within the first year; submit measures and programmatically relevant guidelines to National Quality Forum	CMS (AHRQ, VA, ASPE, AoA)	December 2012
2.G.1	Review evidence on care coordination models for people with AD	Meeting Summary Report	ASPE	December 2012
3.B.1	Identify unmet service needs	Release report summarizing analysis of National Health and Aging Trends Study data	ASPE	December 2012
3.B.2	Identify and disseminate best practices for caregiver assessment and referral through the long-term services and supports system	Explore a public-private partnership to identify best practices in caregiver assessment and referral. This effort will examine caregiver assessment tools used in states, including those used in state Medicaid waiver programs	AoA (private partners)	December 2012
3.C.2	Expand long-term care awareness efforts	Implement awareness campaign	AoA	December 2012
3.D.2	Monitor, report, and reduce inappropriate use of anti-psychotics in nursing homes	Safe Use Initiative	CMS	December 2012
4.B.2	Continue to convene federal partners	Convene federal partners to share research findings, innovative or best practices, and information about new or upcoming initiatives.	ASPE (CDC, NIH/NIA, AoA, CMS, HRSA, AHRQ, IHS, SAMHSA, OASH, VA, NSF, DoD)	December 2012
5.A.2	Identify needed changes or additions to data	Work with federal partners and researchers	ASPE (CMS, CDC, NIH/NIA, AoA, VA)	December 2012
JANUARY - JUNE, 2013				
1.B.1	Expand research to identify the molecular and cellular mechanisms underlying Alzheimer's disease, and translate this information into potential targets for intervention	Develop an integrated interdisciplinary basic science research agenda to enable the identification and selection of therapeutic targets.	NIA/NIH (Potential research partners in the public and private sectors)	January 2013
1.B.2	Expand genetic epidemiologic research to identify risk and protective factors for Alzheimer's disease	Conduct whole genome sequencing to identify areas of genetic variation that correspond to risk factors of AD.	NIH/NIA (Potential research partners in the public and private sectors)	January 2013
1.B.4	Monitor and identify strategies to increase enrollment of racial and ethnic minorities in Alzheimer's disease studies	Track enrollment in NIH Alzheimer's disease studies. Identify and implement next steps for engaging and enhancing research participation by racial and ethnic minorities	NIH	January 2013

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
1.B.5	Conduct clinical trials on the most promising pharmacologic interventions	Identify partnerships with private sector participants for voluntary disclosure of new and ongoing clinical trials; Coordinate federal agencies and private sector to develop cooperative agreement for annual review of the status and progress of the trials and emerging opportunities; review the status and progress of clinical trials annually	NIH/NIA (VA)	January 2013
1.B.6	Continue clinical trials on the most promising lifestyle interventions	Conduct annual reviews of the status and progress of clinical trials.	NIH/NIA (CDC, VA)	January 2013
1.C.1	Identify imaging and biomarkers to monitor disease progression	Conduct annual reviews of Alzheimer's Disease Neuroimaging Initiative (ADNI) to identify and monitor disease progression	NIH/NIA	January 2013
1.E.3	Educate the public about the latest research findings	Prepare and disseminate regular reports on AD research findings	NIH/NIA (NIA Alzheimer's Disease Education and Referral Center, AoA, CDC, FDA, CMS, HRSA, VA)	January 2013
2.H.1	Create a taskforce to improve care for these specific populations	Develop strategic plan with action steps	ASPE, ADD (AoA, CDC, NIH, OD, NIMH)	January 2013
3.B.4	Develop and disseminate evidence-based interventions for people with AD and their caregivers	Identify specific evidence-based interventions that can be developed into training materials or new programs	NIA/NIH (AHRQ, CMS, CDC, AoA)	January 2013
3.C.1	Examine awareness of long-term care needs and barriers to planning for these needs	Finalize Long-Term Care Awareness Survey	ASPE	January 2013
4.A.1	Design and conduct a national education and outreach initiative	Implement national education and outreach initiative	AoA (NIH/NIA, CDC, CMS, HRSA, IHS SAMHSA, OSG)	January 2013
5.B.2	Track plan progress	Track progress on the plan, and incorporate measures into other efforts to monitor population health such as Healthy People 2020. Agency representatives report out biannually after July 2012	ASPE	January 2013
1.E.2	Leverage public and private collaborations to facilitate dissemination, translation, and implementation of research findings	Develop and implement an action plan with milestones and annual evaluation of progress	NIH/NIA (AoA)	February 2013

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
3.B.1	Identify unmet service needs	Convene meetings with state and local officials and stakeholders to identify unmet needs	AoA (ASPE, CDC)	February 2013
2.H.2	Identify steps to ensure access to long-term services and supports for younger people with AD	Coordinate activities to identify barriers to these supports	AoA, OD, ADD (ASPE)	March 2013
3.A.2	Distribute materials to caregivers	Establish a strategy with federal agencies and state and local networks to distribute training and education materials	AoA (CDC)	March 2013
3.E.2	Examine patterns of housing and services	Study where people with AD live and availability of services in those settings	ASPE, NCHS (AoA)	March 2013
3.B.7	Support caregivers in crisis and emergency situations	Webinars with representatives from the aging network, Alzheimer's Disease Centers, and other federal partners	AoA (NIH/NIA)	April 2013
3.C.1	Examine awareness of long-term care needs and barriers to planning for these needs	Conduct survey	ASPE	April 2013
1.A.3	Regularly update the National Plan and refine Goal 1 Strategies and action items based on feedback and input	Update Goal 1 elements of the National Plan to Address Alzheimer's Disease to reflect new insights and input from the community.	HHS/ASPE (NAPA Advisory Council, NIH/NIA and Members of the AD Research Subgroup)	June 2013
2.A.5	Strengthen state aging and public health workforces	Work with state and local health departments to identify public health contributions to cognitive health	CDC	June 2013
2.A.5	Strengthen the state aging and public health workforces	Update the Healthy Brain Initiative Road Map to include strategic actions to align with state plans	CDC	June 2013
3.A.3	Utilize health information technology for caregivers and persons with AD	Convene meeting with stakeholder groups to identify an agenda	AHRQ	June 2013
3.B.4	Develop and disseminate evidence-based interventions for people with AD and their caregivers	Develop training materials and/or design intervention programs based on NIH/NIA research	NIA/NIH (AHRQ, CMS, CDC, AoA)	June 2013
5.B.3	Update the National Plan annually	Release updated National Plan	ASPE	June 2013
JULY - DECEMBER, 2013				
2.H.2	Identify steps to ensure access to long-term services and supports for younger people with AD	Make recommendations to the Advisory Council and HHS on ways to address barriers to supports	AoA, OD, ADD (ASPE)	July 2013
3.A.2	Distribute materials to caregivers	Distribute training materials	AoA	July 2013

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
5.B.2	Track plan progress	Provide summary of data to states that included the BRFSS Cognitive Impairment module	CDC	July 2013
3.C.1	Examine awareness of long-term care needs and barriers to planning for these needs	Release final report of survey results	ASPE	August 2013
3.E.1	Explore affordable housing models	Examine housing sites that link health and long terms services and supports; link HUD and HHS data to understand the older adult population in HUD housing	ASPE, HUD (AoA)	November 2013
1.A.4	Convene a scientific workshop on other dementias in 2013	Hold a workshop to solicit input on special research priorities and timelines for addressing related dementias	NIH (Other Federal funders of dementia research. National and international experts, public and private stakeholders, members of the NAPA Advisory Council on Alzheimer's Research, Care, and Services)	December 2013
1.A.5	Update research priorities and milestones	Updated research priorities and milestones	HHS/ASPE (NAPA Advisory Council, NIH/NIA and Members of the AD Research Subgroup)	December 2013
3.A.3	Utilize health information technology for caregivers and persons with AD	Publish final agenda on health information technology with priority actions	AHRQ	December 2013
JANUARY - JUNE, 2014				
3.B.4	Develop and disseminate evidence-based interventions for people with AD and their caregivers	Conduct a systematic review of evidence-based public health approaches for caregiving	CDC	January 2014
2.C.1	Educate physicians and other health care providers about accessing long-term services and supports	Award grants to disseminate information and increase knowledge of available resources among doctors, nurses, and hospitals.	HRSA (CMS, CDC, NIH/NIA, AoA, VA)	May 2014
2.A.1	Educate health care providers	Educate providers through HRSA's Geriatric Education Centers about how to work with people with the disease, and their families; link people to support services in the community, identify signs of caregiver burden and depression; detect cognitive impairment and assess/diagnose AD	HRSA (CMS-NIA-CDC collaboration (training on helping providers detect cognitive impairment detection in Medicare Annual Wellness Visit)	June 2014

Action Number	Action Description (from Plan)	Method of Action	Lead Agency (Partner Agencies)	Project Completion Date/Status
JULY - DECEMBER, 2014				
3.B.5	Provide effective caregiver interventions through AD-capable systems	AoA will expand efforts to develop more AD-capable long-term services and supports systems designed to meet the needs of AD caregivers	AoA	August 2014
2.F.2	Implement and evaluate new care models to support effective care transitions for people with AD	Evaluate demonstration programs re: hospital admissions, total health care costs, per eligible discharge rate, quality of life indicators, quality of care measures	CMS/CMMI (AoA)	September 2014
5.A.3	Make needed improvements to data	Develop questions to be fielded for data collection; add to surveys	ASPE (NCHS/CDC, NIH/NIA)	December 2014
2015				
2.E.1	Evaluate the effectiveness of medical home models for people with AD	Examine changes in care quality and care coordination among people with AD to explore whether these models lead to more effective and efficient care.	CMS/CMMI	July 2015
2.E.2	Evaluate the effectiveness of the Independence at Home Demonstration	Examine whether health and functional status outcomes are improved among people with AD in this demonstration.	CMS/CMMI	July 2015
2.F.1	Explore the effects of new payment models on AD care and costs.	Perform subgroup analysis of CMMI models	CMS/CMMI	July 2015
2.G.2	Consider test of new payment or delivery model to promote the quality of AD care while reducing costs	New models for consideration by the CMMI portfolio committee.	CMS/CMMI	July 2015

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