2. SPECIFIC AIMS

In the initial funding period (9/30/05 to 6/30/10) for this program project, "Antecedent Biomarkers for AD: The Adult Children Study" (ACS), we aimed to establish a unique cohort of cognitively normal middle age individuals who were eligible for and willing to participate in an extensive study of biomarkers for Alzheimer's disease (AD), prior to its symptomatic stages. This new scientific initiative was the logical "next step" for our research program, which for years has explored the correlates of preclinical AD in cognitively healthy older adults, as supported by our ADRc and particularly by our other program project, "Healthy Aging and Senile Dementia" (HASD). Indeed, HASD was the direct "parent" for ACS: 3 of the 4 original projects in ACS were identical in leadership and scientific goals to projects in HASD in its equivalent funding period (1/1/04 to 12/31/08), the difference being HASD studied older adults whereas ACS studied middle age adults. Fifty percent of the ACS cohort is at increased risk for AD by virtue of having a biologic parent with AD.

The premise for ACS was and is that AD has a lengthy period in which cerebral lesions gradually accumulate in the absence of symptoms (i.e., preclinical AD) but eventually these lesions cause sufficient synaptic and neuronal damage to result in symptomatic AD. Realizing that we could not test this premise in the initial funding period because of an insufficient follow-up period, we planned a cross-sectional study to examine the hypothesis that preclinical AD can be detected in some cognitively normal individuals age 45 to 74 years. We employed a broad array of candidate antecedent biomarkers for AD, including clinical and cognitive measures, structural neuroimaging with magnetic resonance imaging (MRI), biofluid assays (blood; cerebrospinal fluid [CSF]), and molecular imaging of fibrillar amyloid with positron emission tomography (PET) using the [^{11}C] benzothiazole tracer, Pittsburgh Compound-B (PIB). Both the enrollment of the ACS cohort and the detection of preclinical AD were successfully accomplished in the original funding period.

In this application, we take another logical "next step". We now transition from a cross-sectional to a longitudinal biomarker study in the ACS cohort, and also add functional imaging measures to the other biomarker modalities. The overarching aim of this application is to expand knowledge about preclinical AD, and specifically to characterize the chronology of biomarker changes, determine their pathobiological signatures, and identify cognitively normal persons who are at very high risk for developing symptomatic AD.

The overall Specific Aims in this renewal application are to:

1. Follow the current participants in ACS and add new enrollees to maintain the sample size at ~300.
2. Obtain longitudinal data from the ACS participants at 2 year intervals with the following measures:
   a. Clinical and cognitive assessments (Clinical Core); participants ≥ 65 years are assessed annually with these measures.
   b. Amyloid imaging with PET PIB (Project 1)
   c. Assays of amyloid-beta (Aβ), tau, phosphorylated tau_{181} (p-tau_{181}), and novel analytes in CSF and blood (Project 2, supported by the Biomarker Core)
   d. Attentional control battery and task-related functional MRI (fMRI) (Project 3)
   e. Structural MRI, resting state functional connectivity MRI (fcMRI), diffusion tensor imaging (DTI), and cerebral blood flow using arterial spin labeling (ASL) (Project 4)
3. Analyze associations among rates of change of all disease markers from all Cores and Projects (Data Management and Biostatistics Core).

3. RESEARCH STRATEGY

Glossary of Terms

WU/WUSM: Washington University/Washington University School of Medicine

ADRC: Alzheimer Disease Research Center (P50 AG05681). The ADRC received in 2010 an endowment gift from benefactors Charles and Joanne Knight and now is named the Knight ADRC in their honor.

DAT: Dementia of the Alzheimer Type. Criteria for the clinical diagnosis of Alzheimer disease (AD) are being revised in the proposed DSMV and the updated NINDS-ADRDA criteria. Moreover, the conceptualization of mild cognitive impairment (MCI) is moving toward a more etiological basis (e.g., MCI due to AD), and the determination of when this prodromal stage of AD meets conventional criteria for dementia remains dependent on clinical judgment. Hence, "DAT" may become outmoded in future years as previous concepts are revised in accordance with new knowledge and thinking. This PPG continues to refer to "DAT" but also uses the term "symptomatic AD" to capture the earliest stages of clinically detectable cognitive change caused by AD. **Symptomatic AD** thus encompasses prodromal stages such as MCI due to AD as well as the more overt stages of Alzheimer dementia. Presymptomatic AD is the pathologic process absent any clinically detectable symptoms, and here is synonymous with **preclinical AD**.

CDR: Clinical Dementia Rating. In this application, CDR=0 indicates cognitive normality and CDR>0 indicates clinically determined cognitive impairment. Not all cognitive impairment designated by CDR>0 necessarily is attributable to AD.

MAP: Memory and Aging Project, the clinical research office where since 1979 all clinical and psychometric assessments are conducted for participants in all our longitudinal studies of aging and dementia, including ACS participants. In 2008, a satellite MAP office ("West County") was established.

SIGNIFICANCE

AD is by far the most common neurodegenerative dementing disorder.[1] In 2005, the total costs to Medicare, Medicaid, and businesses for care of beneficiaries with dementia were $148 billion.[2] In the absence of effective treatments, the social and public health costs of AD will continue to rise annually as dementia prevalence increases with the aging population.

There is much evidence to support the hypothesis that accumulation of the Aβ peptide, typically found aggregated in brain parenchyma as senile plaques, is a primary mechanism in the pathogenesis of AD.[3] However, candidate "disease-modifying" drugs that target Aβ have yet to demonstrate efficacy in persons with symptomatic AD, even when it appears that the treatment may succeed in reducing cerebral Aβ burden.[4] It is possible that the failure to date of anti-Aβ monotherapies to benefit individuals with clinically diagnosed AD has occurred because the treatments were administered too late in the disease process. That is, although Aβ dysregulation may initiate the pathogenesis of AD, it likely is followed by a cascade of downstream factors that exacerbate and propagate neuronal injury.[5] (Figure 1) The optimal window of opportunity for anti-Aβ therapies thus may be very early in the pathologic course of AD, before the presence of substantial synaptic and neuronal damage. This explanation fits well with the concept of preclinical AD.[6-8] The preclinical stage of AD may last for years or even decades and may be unaccompanied by substantial neuronal damage for much of this period, making preclinical AD an attractive target for potential primary prevention

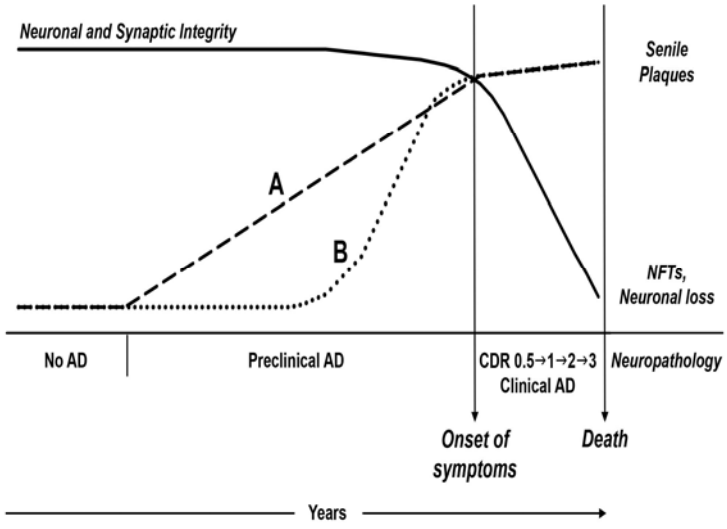


Figure 1. Models of Aβ accumulation over the hypothetical time course of pathologic changes in preclinical AD and symptomatic AD.The dashed line (A) represents linear Aβ accumulation (beginning ~20-25 yr before symptom onset) and the dotted line (B) represents nonlinear Aβ accumulation (beginning ~10 yr before symptom onset).(Other trajectories are possible.) Biomarkers for Aβ are [^{11}C]PIB and reduced CSF $A\beta_{42}$. Markers of neuronal/synaptic integrity include elevated CSF tau/p-tau, regional and whole brain volumetry, functional brain abnormalities, cognitive dysfunction and decline, and dementia and disability.

trials for AD. Candidate therapies for such trials include several anti-Aβ strategies, but the dynamics of Aβ deposition during preclinical AD are unknown. Elucidating the natural history of preclinical AD has great importance for the understanding of the pathophysiology of AD.[9]

Other neurotoxic factors may have important roles in preclinical AD. These factors potentially include soluble forms of Aβ, gliosis and other inflammatory responses, cell cycle abnormalities, oxidative stress, and the second fundamental neuropathologic feature of AD, hyperphosphorylated tau in the form of neurofibrillary tangles (NFTs) and dystrophic neurites.[10] Several findings, however, suggest that neocortical neurofibrillary change occurs downstream of Aβ accumulation. Outside of medial temporal structures where NFTs appear to accumulate as a function of age, there is an increased presence of NFTs in preclinical AD only after Aβ deposition has occurred.[6] Similarly, elevated levels of Aβ peptides in the frontal cortex occur very early in the pathologic process of AD, prior to significant tau pathology.[11] We recently reported that CSF levels of tau and $ptau_{181}$ are not associated with structural brain changes in individuals with preclinical AD, whereas reduced levels of CSF $A\beta_{42}$ in the same individuals are associated with whole brain atrophy.[12] Such observations are consistent with a central and early role for Aβ accumulation in preclinical AD, preceding substantial NFT accumulation and other indicators of neuronal and synaptic damage which appear to mark the transition from preclinical to symptomatic AD.[12,13]

Table 1: Percent of Cognitively Normal Individuals with Abnormal PET PIB or CSF $A\beta_{42}$ Values

Age Range	Elevated MCBP	Reduced CSF $A\beta_{42}$
50-59y	5.7%	14.0%
60-69y	19.0%	27.1%
70-79y	25.8%	34.2%

These preliminary findings notwithstanding, however, the current state of knowledge about the sequence and chronology of the pathophysiologic events in preclinical AD is woefully inadequate. **The Significance of this application is that the cognitively normal middle age participants followed in the ACS represent the ideal cohort for a longitudinal study of the rate of occurrence of preclinical AD, the identification of factors that mediate its occurrence, and its structural, functional, and behavioral correlates.** The ACS participants are enrolled in the age range (45y-74y) during which preclinical AD is predicted to appear, are exceptionally dedicated to research with high completion rates of all procedures, and participate fully in all aspects of the ACS longitudinal protocol. This protocol includes clinical and cognitive assessments, amyloid imaging with PET PIB, structural and functional MRI, and lumbar puncture (LP) for CSF collection, thus permitting correlations of biomarker data obtained in all ACS projects and cores from the same individuals. **Importantly, we know from our current cross-sectional studies that preclinical AD (as detected by biomarker changes) is present in a sizeable proportion of ACS participants** (Table 1).[14] This remarkable cohort uniquely positions the ACS to achieve its aims of characterizing preclinical AD. Not only will it provide heretofore unavailable insights regarding the evolution of biomarker changes during the course of preclinical AD, it also will provide information regarding the potential utility of these changes for the design and evaluation of potential "disease-modifying" therapies for AD, including primary prevention trials.

INNOVATION

The ACS examines indicators of preclinical AD using a cohort of cognitively normal middle age individuals who longitudinally complete an extensive array of biomarker assays, including CSF studies. Given the absence of prior experience (e.g., few or no similar studies) from which we might benefit, we must pioneer new methods to achieve our goals, such as the serial collection of CSF solely for research purposes in healthy middle age individuals. The ACS does benefit enormously, however, from the presence of our ADRC and HASD, in that together they provide the scientific foundation for this application as well as valuable infrastructure and other support. The ACS capitalizes on the investigators, staff, methods, and procedures that work smoothly in these established and successful programs. For example, the ADRC's Genetics Core performs at cost the apolipoprotein E genotyping for ACS participants. Because the ACS uses the recruitment, enrollment, and clinical and cognitive assessment procedures that were developed in HASD/ADRC, and because we standardized our imaging and biofluid protocols across all of our grants, the findings obtained in ACS can be directly compared and correlated with those obtained in HASD/ADRC. This innovative interlinkage of the cohorts studied under 3 grant mechanisms effectively allows a combined cohort of 811 individuals (283 ACS, 219 HASD, 309 ADRC), ranging in age from 45 years (the youngest age in ACS) to 100 years (the oldest active participant in ADRC).

[Note: Each grant is budgetarily distinct from the others. The assessment protocols intentionally are identical (with the exception that ACS participants, because of their younger age, are administered additional cognitive measures that are not given to ADRC or HASD participants) and are conducted by the same personnel. The

uniform assessment promotes synergism by allowing participants and their data from one grant to be available for projects supported by another grant. However, ACS participant enrollment and expenses and associated reporting are linked directly and only to the ACS grant. All budgetary aspects described in this competitive renewal application are unique to ACS.]

APPROACH

Progress Report for Program Project as a Whole

Response to Summary Statement (2005)

Overall weakness identified in the application for the first funding period are provided here with our responses.

1. *"Inadequate attention to statistical issues in this complex study".* We are establishing with this application the new Data Management and Biostatistics Core (DMBC) with a budget that is increased more than 33% over the current biostatistics budget, which had been included in the Administration Core. [*In addition, institutional funds will support a new, full-time statistical data analyst for the ACS DMBC*.] Moreover, the DMBC Leader, Dr. Xiong, has obtained extensive experience in sophisticated longitudinal statistical methods.

2. "Lack of a unifying disease model to focus cross-project analyses". See Figure 1.

3. "Interpretative difficulties when disease risk and pathology are undetermined". Table 1 now lists the frequency of preclinical AD, as detected by biomarkers, in the ACS cohort by age range.

4. "Variable validation of proposed biomarkers". ACS provides the opportunity to validate biomarkers, particularly for prognosis (i.e., conversion from cognitively normal status to symptomatic AD). We have preliminary data to support both CSF measures of $A\beta_{42}$ and tau and PET PIB as prognostic biomarkers[15,16]

5. "Incomplete integration across projects, including for analyses". The projects in this application are well-integrated. For example, the regions of interest generated by Project 4 will be transferred to Project 1 for exploratory analyses of regional PIB levels; Project 4 will conduct the task-based fMRI for Project 3; and there are many examples in our publications[12,14-19] of correlations of biomarker data across projects. [*A recent example is shown in our study of cognitively normal participants who had no evidence of cerebral amyloid deposits as determined by PET PIB and by CSF $A\beta_{42}$ levels; functional connectivity assessed by fcMRI was disrupted in the default mode network as a function of APOE4 carrier status.[20] This study thus utilized Project 1 (PET PIB), Project 2 (CSF $A\beta_{42}$), Project 4 (fcMRI), and Clinical Core (cognitive normality) data along with genotyping by the Genetics Core of the Knight ADRC to demonstrate genetic effect for functional connectivity prior to overt Aβ abnormalities or cognitive changes, thus identifying another potential biomarker of preclinical AD that will be further explored in Project 4 of this application.]*

In contributing to the analytic plans for each Project in this application, Dr. Xiong specifically included plans for integrated analyses. Additionally, all biomarker assessments will be obtained at a 2 year interval.

6. "Lack of pilot data to drive power calculations". The cross-sectional analyses of the original funding period now provide such data (e.g., Table 1).

7. "Insufficient consideration of APOE and family history interactions". Baseline data from 269 ACS participants were analyzed to determine whether family history (FH) conveys risk for AD beyond that associated with apolipoprotein Eε4 (APOE4). Using analysis of covariance, age-related changes (if any) of the cognitive, imaging, and CSF biomarkers or age-adjusted means of these markers were examined for associations with FH and APOE. Effects of FH independent of APOE were found for several biomarkers, including CSF $A\beta_{42}$, fractional anisotropy, and radial diffusivity (diffusion tensor imaging). These results indicate that nonAPOE4 susceptibility factors can increase risk for abnormal AD biomarkers, has been demonstrated in other studies of preclinical AD[21,22] and as as would be expected from recent identification of several risk genes (e.g., *CRU, CR1, PICALM, SORL1)* for AD.[23] The manuscript reporting these findings is under revision. Hence, we continue to stratify the ACS cohort on parental history of AD.

8. "Insufficient consideration of factors such as aging and environment". There is an age effect on our biomarker abnormalities (Table 1)[14] and in this application Project 1 examines environmental and lifestyle factors important for "reserve".

Organization of the ACS PPG

The organizational structure of ACS in this application compared with the last one is shown in Table 2.

Table 2. Antecedent Biomarkers for AD: The Adult Children Study

2005-2010	2011-2016
Core A: Administration (PI-Morris)	Core A: Administration (PI-Morris)
Core B: Clinical (CL-Morris)	Core B: Clinical (CL-Morris)
Core C: Biomarker (competitive supplmt) (CL-Fagan)	Core C: Biomarker (CL, Fagan)
	Core D: Data Management & Biostatistics (CL,Xiong)
Project 1: Amyloid Imaging in the Adult Children Study (PL, Morris)	Project 1: The Natural History of Aβ Accumulation in Preclinical AD (PL, Morris)
Project 2: CSF Biomarkers of Antecedent AD (PL-Fagan)	Project 2: CSF Biomarkers of Antecedent AD (PL-Fagan)
Project 3: Attentional Profiles as an Early Marker for DAT (PL-Balota)	Project 3: Behavioral and Neural Markers of Attentional Control: Antecedents for AD (PL-Balota)
Project 4: Neuroanatomical Biomarkers of Early AD (PL-Csernansky)	Project 4: Antecedent Neuroimaging Biomarkers (PL-Benzinger)
Project 5: Amyloid-Beta Metabolism in Familial Adult Children Study (competitive supplmt) (PL-Bateman)	

Major changes for this application are discussed here.

1. Establish the DMBC (see response 1. in Response to 2005 Summary Statement, above).
2. Although Project 4 in this application continues to assess structural brain changes with MRI, it has changed leadership (the original Project 4 Leader, John Csernansky, MD, left Washington University in 2008 to become Chair of the Department of Psychiatry at Northwestern University). This provided the opportunity for ACS to engage Tammie Benzinger, MD, PhD, assistant professor in the Department of Radiology at Washington University where she is clinical director of neuromagnetic resonance imaging. Dr. Benzinger's research focuses on the applications of advanced and novel neuroimaging techniques in human diseases, and she proposes to expand Project 4 with the inclusion of new measures to assess structure (e.g., DTI) and brain function, including fcMRI and cerebral blood flow using ASL. This later technique is being used extensively in the study of neurological diseases by Beau Ances, MD, PhD, a recent addition to the Department of Neurology and now a Project 4 investigator. We thus benefit in Project 4 in this application by attracting highly promising junior faculty such as Drs. Benzinger and Ances to AD research and at the same time support them with the experience and expertise of 4 established investigators, Drs. Mark Mintun, Marc Raichle, Abraham Z. Snyder, and Yvette Sheline.
3. During the original funding period, ACS submitted two competing supplements and was fortunate in having both awarded. One established the Biomarkers Core (A. Fagan, Core Leader) for ACS and will continue under Dr. Fagan's leadership in this application. The other established Project 5, led by Dr. Randall Bateman, to conduct an amyloid metabolism study of individuals who are adult children of a parent with a known deterministic mutation for AD (i.e., in the *APP*, *PSEN1*, or *PSEN2* genes). The platform provided by Project 5 and by the ACS in general led to a subsequent application in response to RFA AG-08-002, which we also were fortunate to be awarded as the Dominantly Inherited Alzheimer's Network (DIAN). Hence, ACS Project 5 does not continue in this application as the Project 5 participants all migrated to DIAN at the end of the current ACS funding period (6/30/10).
4. Another change in this application is the shift from cross-sectional to longitudinal analyses of the ACS data.

PROGRESS REPORT (2005-2010) [Note: The ACS has been productive in the current funding period, and the Summary Publications number 82. Only a few publications are selected for review here (5-8, below)]

1. Awarded two competing supplemental applications to establish the Biomarkers Core and Project 5, The Familial Adult Children Study (see 3. Changes, above).
2. The ACS was leveraged successfully to establish DIAN (see 3. Changes, above).
3. The Clinical Core exceeded its goal of enrolling 240 cognitively normal ACS participants, ages 45-75 years at entry (120 with a biologic parent with AD, 120 for whom neither parent had AD); a total of 283 were enrolled. Seventy-four percent (n=209) of the participants completed all 6 baseline procedures: clinical assessment, psychometrics, PET PIB, CSF collection, attentional battery, and MRI. Ninety-five percent completed 4 or more of the procedures. There remain 258 active ACS participants who will continue in this application; of the remaining 25, 23 have been attritioned (primarily because they decline to participate in biomarker studies) and

2 have died (one autopsy). The active participants are in the process of completing their follow-up assessments and procedures (see Table 2 of Clinical Core). [Note: Project 5 participants are not included in the reported numbers of ACS participants as their genetic risk for AD is different than for ACS participants.]
4. Since its inception in 2008, the Biomarkers Core has banked 10,700 aliquots of CSF from 183 individuals and 6,400 aliquots of fasted plasma. The Core has provided 2,300 CSF and 200 plasma samples to non-ACS investigators, both internal and external to Washington University. This remarkable tissue repository will become even more valuable as longitudinal samples, obtained with this application, are added.
5. There is an inverse relationship of elevated levels of PIB in cerebral cortex with CSF levels of Aβ42.[17] All PIB-positive individuals have low CSF levels of $A\beta_{42}$; however, some PIB-negative individuals have low levels of CSF $A\beta_{42}$.[18] This finding is consistent with a hypothetical sequence of biomarker abnormalities in preclinical AD where reductions in CSF $A\beta_{42}$ levels precede fibrillar Aβ deposition in cerebral cortex. Support for this sequence comes from a HASD participant, followed with PET PIB and CSF as well as cognitive measures until coming to autopsy.[13]
6. The frequency of cognitively normal individuals with elevated PIB levels and with reductions of CSF $A\beta_{42}$ levels increases as a function of age and APOE4 genotype.[14] There is a protective effect of APOE2, such that there is negligible or no PIB increase (or CSF $A\beta_{42}$ reductions) in APOE2 carriers.[14] There is no relation of APOE genotype for CSF tau or p-tau_{181} levels.
7. Preclinical AD, as detected by imaging and CSF biomarkers, has pathobiological signatures. Cognitively normal individuals with low levels of CSF $A\beta_{42}$ have smaller whole brain volumes than individuals with normal levels; there is no association of whole brain volumes with CSF tau or ptau_{181} levels in cognitively normal persons.[12] Opposite relationships are seen for individuals with DAT (from HASD/ADRC): there is no relationship of brain volume with CSF $A\beta_{42}$, but smaller brain volumes are seen for individuals with elevated CSF tau or p-tau_{181}. These observations are consistent with the presence of deleterious effects of $A\beta_{42}$ for brain health during the preclinical (cognitively normal) stage of AD. When sufficient neurodegeneration occurs to result in symptomatic AD, then tau effects are observed.
Cognitively normal PIB-positive individuals, in comparison with PIB-negative individuals, have regional volumetric changes in the hippocampus, temporal neocortex, anterior cingulate, and posterior cingulate.[19] In longitudinal analyses, the slopes for measures of working memory and visuospatial function were significantly downward in the years before the positive PIB scan was obtained.
8. In cognitively normal individuals, elevated PIB levels or a high ratio of CSF tau or p-tau_{181} to CSF $A\beta_{42}$ predict the development of symptomatic AD in 3-4 years.[15,16] Both studies had small sample sizes and must be considered as preliminary, but they provide support for the hypothesis that preclinical AD, as detected by CSF and imaging biomarkers, is likely to be associated with subsequent symptomatic AD.
9. Project 4 in the current funding period is continuing under new leadership in this application. Progress in this funding period overcame a change in MR scanner field strengths. In years 1 and 2, 79 ACS individuals had been imaged with a 1.5T scanner, and 167 subsequently with a 3T scanner (through 12/11/09). To date, we have not found differences in high dimensional diffeomorphic maps of the hippocampus between ACS participants with and without a parental history of AD, but brain structural changes have been associated with CSF and imaging biomarkers of preclinical AD.[12,19]

COHERENCE

The multidisciplinary ACS team of investigators is highly collaborative and well-integrated. The stability of this team (Table 2, above) attests to its coherence. Virtually all publications coming from the ACS include data from multiple ACS projects and correspondingly are appropriately co-authored by multiple investigators (see Summary Publication List). Dr. Morris, ACS PI, has interacted productively for over 16 years with Drs. Fagan and Holtzman (Project 2), 19 years with Dr. Buckles (Administration Core), 23 years with Drs. Balota and Duchek (Project 4), and 27 years with Dr. Grant (DMBC) and Dr. Storandt (Clinical Core). He has authored or co-authored papers with each ACS investigator in this application, with the exception of Dr. Zacks. The team meets formally every 2 months as an executive committee to review and discuss progress toward goals but in actuality subgroups of ACS investigators meet almost daily regarding ACS data and analyses. The team as a whole has met repeatedly, beginning in June 2009, to plan and develop this application.

The foundation of the ACS is the Clinical Core and its longitudinally studied ACS cohort. The Core provides participants to all Projects. The Biomarker Core collects and maintains CSF and plasma from ACS participants, provides samples to Project 2 for assays of $A\beta_{42}$, tau, p-tau_{181}, and novel biomarker proteins for AD, and supports data sharing of CSF values across all Projects. It also serves as the biospecimen repository

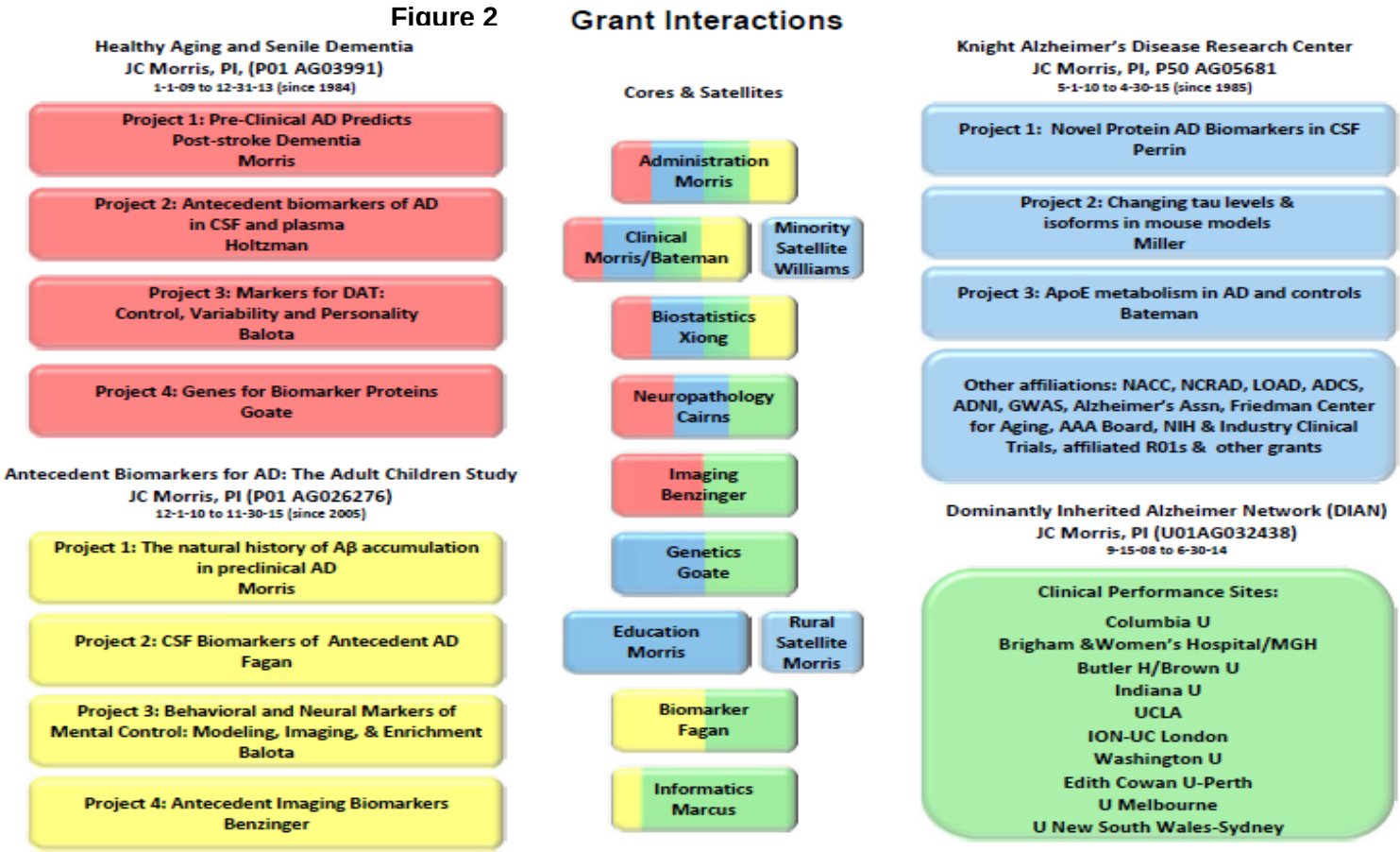
for ACS. The Administration Core and DMBC interact regularly with all ACS investigators and Projects and were directly involved in the preparation of each component of this application. The aims of each Project are organized around the central theme of the ACS: the characterization of preclinical AD using clinical, cognitive, imaging, and biofluid biomarkers and elucidating its pathobiological correlates. Each Project uses specific approaches to address this theme, but these approaches are interdependent. The understanding of the sequence and chronology of biomarker changes indicating preclinical AD can only be appreciated by combining data from multiple modalities (i.e., across the Projects). To facilitate these cross-Project data analyses, beginning with this application, the Cores and Projects have adopted a uniform interval of every 2 years for all follow-up procedures. The example given above (Progress Report) of ACS participants with reduced CSF $A\beta_{42}$ levels (Project 2) in the absence of elevated PIB levels (Project 1) illustrates how data integration is critical to appreciate the natural history of preclinical AD.

INTERRELATIONSHIPS

Externally funded longitudinal research studies on aging and dementia at WUSM began in 1979 under the direction of Leonard Berg, MD, and these studies were the direct forbearers of HASD (initiated in 1984), ADRC (1985), ACS (2005), and DIAN (2008). The interlinkages and integration of these programs is discussed in Innovation (above), and the overarching administrative structure for these programs is shown below in Figure 2. All grants currently are led by Dr. Morris, who succeeded Dr. Berg as program director in 1998, and the executive director for each is Dr. Buckles. Dr. Xiong leads the Data Management and Biostatistics components for each grant, providing additional integration for these programs.

Drs. Morris and Buckles are faculty in the Department of Neurology, where the head of the Department is Dr. Holtzman (see Letter of Support, LOS), who also serves as an ACS investigator (Project 2). The ACS is highly regarded at Washington University and receives outstanding institutional support, not only from Neurology (LOS from Dr. Holtzman) but also Radiology (LOS from Dr. Gilbert Jost, Chair), the Division of Biostatistics (LOS from Dr. DC Rao, Chair) the School of Medicine (LOS from Dr. Larry Shapiro, Dean), and the University as a whole (LOS from Dr. Mark Wrighton, Chancellor).

Figure 2



4. Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: Antecedent Biomarker for AD: The Adult Children Study

Total Enrollment: 283 **Protocol Number:**

Grant Number: P01AG026276

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Females	Males	Sex/Gender Unknown or Not Reported	Total
Hispanic or Latino	0	0	0	0 **
Not Hispanic or Latino	192	91	0	283
Unknown (individuals not reporting ethnicity)	0	0	0	0
Ethnic Category: Total of All Subjects*	192	91	0	283 *
Racial Categories				
American Indian/Alaska Native	0	0	0	0
Asian	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	27	10	0	37
White	162	81	0	243
More Than One Race	2	0	0	2
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of All Subjects*	192	91	0	283 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Sex/Gender Unknown or Not Reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	0	0	0	0
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of Hispanics or Latinos**	0	0	0	0 **

* These totals must agree.
** These totals must agree.

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Submitted

1. Ances BM, Rich P, Thomas J, Snyder AZ, Peng H, Benzinger T, Duchek J, Mintun M, Morris JC, Balota D. Resting state blood oxygen level dependent functional connectivity and stroop task coefficient of variance (COV) as early biomarkers of dementia of Alzheimer's type, submitted
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4. Wang L, Fagan AM, Shah AR, Beg F, Holtzman DM, Miller JP, Morris JC, Csernansky JG. CSF proteins predict hippocampal degeneration in early stage Alzheimer's dementia, submitted.
5. Xiong C, Roe C, Buckles V, Fagan A, Holtzman D, Balota D, Duchek J, Storandt M, Mintun M, Grant E, Snyder A, Head D, Benzinger T, Mettenburg J, Csernansky J, Morris J, Family history of Alzheimer disease influences biomarker abnormalities in the Adult Children Study, submitted.

6. PROTECTION OF HUMAN SUBJECTS

A**.** RISKS TO HUMAN SUBJECTS

Human Subjects Involvement and Characteristics, and Design:

Participants are recruited from the greater metropolitan St. Louis area (population 2.8 million). There is no billing of participants, their families, or third party payers for research assessments or participation. During the 5 years of this renewal application the Core will be following an active pool of approximately 258 already enrolled participants and recruit an additional 75 cognitively healthy (CDR 0) individuals to meet the needs of the Cores and Projects and replace participants who have attritioned from the study. The goal is to enroll at least 50 active participants in each of the age ranges in each family history group (n=50 age 55-64y, n=50 age 55-64y, n=50 age 65-75y). Participants age 45-64 will undergo comprehensive clinical assessments every 4 years. A brief interview of the Collateral Source (the AD8; see Clinical Core) and the full psychometric battery will be obtained at year 2 in this 4 year interval; hence, cognitive assessments are obtained on the same 2 year interval as for all other biomarkers. [Note: If the AD8 suggests clinical impairment, the participant then is scheduled for the comprehensive clinical assessment.] Once participants reach age 65 both comprehensive clinical and psychometric assessments are obtained annually. Participants are recruited from the community primarily by means of word of mouth and public service announcements. Both sexes are enrolled without regard to race, ethnicity, or religion. The composition of participants enrolled in during the current funding period is 68% female and 87% white; 13% are African American (18% of the population in the greater St. Louis area is African American, which is by far the largest minority group in St. Louis).

Inclusion criteria: Participants will be healthy and cognitively normal. They have a family history of DAT, defined as being a biologic child of at least one parent with DAT before age 80 (verified by MAP or by medical records), **OR** have no family history of DAT, defined as being the biologic child of parents who have never developed DAT and lived to age 70 or beyond. Participants have the intention of participating in all assessments and procedures in the study. See the Inclusion Enrollment Report for the Gender and Minority Recruitment since the last competitive renewal.

Exclusion criteria: Potentially dementing, neurologic, medical, or psychiatric conditions and medical contraindications for the proposed studies of this PPG (e.g. pacemaker for MRI, anticoagulant use for the LP) are exclusionary.

Source of Materials:

Research material obtained from participants consists of clinical, psychometric, physical/neurological, and personality/behavioral data regarding cognitive health. Existing medical records are requested with usual authorization for review related to co-morbid conditions and study eligibility. Nonfasted blood specimens (20cc obtained by venipuncture) for APOE genotyping and other genetic studies are collected at initial assessment. We comply with the NIA Biospecimen Best Practice Guidelines for the ADRCs. These data (including APOE genotype) are used for research purposes only; individual results are not provided to participants, their families, or their physicians. This policy is waived in the event of immediate potential danger to the

participant's health (e.g. acute suicidal ideation) or a clinically meaningful abnormality detected by testing (e.g. MRI abnormality). Such information is divulged to participants by the Clinical Core Leader and, with their permission, to their physician. There is no billing of insurance companies or Medicare.

Potential Risks:

Potential risks are few and minor. The Clinical Core's research procedures consist of history taking, videotaping of interviews, a brief physical/neurological examination, and psychometric testing. Slight bruising or discomfort potentially may occur at the venipuncture site. Embarrassment could occur should participants believe they answer questions incorrectly. Empathetic and professional Clinical Core staff mitigate the risk of embarrassment. Venipuncture is accomplished by experienced Clinical Core nurse clinicians. No alternative methods are available to gather comparable data. There is potential negative impact on employment, insurability, or other factors for an individual participating in research studies of "memory and aging". Information about participation is not divulged to any outside party, unless a summary of the clinical assessment for the participant's personal physician is requested in writing by the participant after full disclosure of potential risks. As noted above, specific research data are not divulged.

B. ADEQUACY OF PROTECTION AGAINST RISK

Recruitment and Informed Consent. The children of our past and present research participants are recruited via our annual Participants' Meeting, ADRC Newsletter and the ACS Brochure (Appendix). Also, participant recruitment occurs through public service announcements (radio, television, and print media), requests to private physicians, and organizations (e.g., the St. Louis Chapter of the Alzheimer's Association, Washington University Volunteers for Health) and word of mouth. All recruitment materials are approved by the Washington University Human Research Protection Office (HRPO) prior to use.

The cornerstone of protection in research is informed consent. The ACS consent form is included with the appointment letter sent to the participant for review prior to the initial visit for the clinical assessment. The initial visit to the ADRC begins with a half hour explanation hour ("the Intake") of the nature of research participation and discussion of the risks and benefits of participation by the ACS coordinator (or, in her absence, the ACS nurse) with the participant and the collateral source (CS). The CS is a person who knows the participant well and most often is the spouse or the adult child of the participant. (Other individuals serving as CSs include siblings, adult grandchildren, companions, and friends). We have a policy of "dual consent" where the CS signs the consent as well as the participant. The original signed consent forms are kept with the participant's confidential file and a copy is given to the participant. We have separate informed consent documents (Appendix), one for participation in the clinical, cognitive and neurological/physical examination, and the other for participation in the genetic studies (APOE genotyping; DNA). There has been no modification of waiver of these procedures.

Future use of Data/Data Sharing. Several important elements included in the consent form and are emphasized in the Intake. These include: 1) the information collected in the assessment is saved indefinitely to be used by researchers at Washington University or investigators outside the University now and in the future to answer questions about memory, thinking, aging and other dementing illnesses; 2) prospective authorization for continued participation, even if the person loses the ability to make decisions related to research participation. In the consent form used to obtain blood for genetic studies (See Appendix) participants waive their claim to the blood or products resulting from the blood. Specific attention is drawn to information that blood is frozen, stored indefinitely, and potentially shared with other investigators.

Protection Against Risk. All data are safeguarded in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the principles and practices of strict confidentiality. Studies are done for research purposes only. Data from the assessment is shared with ACS-approved investigators. Data are maintained by numerical code rather than personal identifiers. All data (including diagnostic information) are protected. The participant can request that a brief summary (usually a single paragraph) of the clinical assessment be sent to their physician but we do not release specific data or results. The risk of having the summary in the medical record (in the participant's private physician's office) is explained on the medical record release form and in the consent form. No report is generated about participation in genetic studies and nor is such participation included in the clinical summary paragraph sent to the private physician.

Durable Power of Attorney/Research Proxy (DPOA). At each clinical assessment we confirm the information we have regarding the participant's designation of a DPOA for health care. The name and contact information for the DPOA is included in the research files. If a DPOA has been designated we include a copy of the document in our files. If the participant does not have a DPOA we give them information about DPOA

and how it can be obtained. Also, we ask each participant to designate a Research Proxy (see Appendix) because the DPOA documents seldom specifically mention research decisions.

C. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE PARTICIPANTS AND OTHERS

Potentially, participants benefit through comprehensive evaluation of memory and thinking. They will be given feedback about the findings of the clinical assessment and recommendations when appropriate. Diagnosis/treatment of an urgent clinical condition occurs when indicated. The participant is informed of treatment options and resources available through community agencies.

D. IMPORTANCE OF KNOWLEDGE TO BE GAINED

Society will benefit from advances in knowledge of developing indicators or biomarkers that may detect persons who will develop AD in the future. As potential disease-modifying or preventative therapeutic strategies are developed, they may have optimal benefit in nondemented individuals who are identified to be at high risk for DAT and diagnostic strategies proposed by these studies. In relation to these anticipated benefits and the importance of knowledge to be gained, the minimal risks involved in this research are reasonable.

Institutional Review Board Approvals:

Project Title: Antecedent Biomarkers for AD: The Adult Children Study: P01AG026276, JC Morris, PI				
Human Research Protection Office Approvals				
Principal Investigator	TITLE OF EACH PROJECT	HSC #	Approval Date	Page # of Human Studies Section
Morris, John C.	Core B: Clinical	10-0554	07/07/10	128
Niven, Anne Fagan	Core C: Biomarkers	97-0835	10/28/10	162
Xiong, Chengjie	Core D: Data Management & Biostatistics	10-1178	10/13/10	191
Morris, John C.	Project 1: The Natural History of Aβ Accumulation in Preclinical AD	05-0826	07/15/10	238
Niven, Anne Fagan	Project 2: CSF biomarkers of antecedent AD	97-0835	10/28/10	273
Balota, David	Project 3: Behavioral and Neural Markers of Attentional Control: Antecedents for AD	97-0674	04/22/10	321
Benzinger, Tammie	Project 4: Antecedent Neuroimaging Biomarkers	05-0673	07/15/10	378

7. INCLUSION OF WOMEN AND MINORITIES:

6a. Inclusion of Women. Women are included in all studies described. Approximately 68% of the participants are women.

6b. Inclusion of minorities: All minority groups are encouraged to participate in this research. Intensive ongoing efforts by the African American Outreach Satellite and Education Core of the Knight ADRC and the ACS Clinical Core focus on recruitment of African Americans, the largest minority population in the community. The Knight ADRC's African American Advisory Board, consisting of representatives of the African American lay and academic community, advises the Core about recruitment activities and materials to be utilized to diversify the sample.

8. Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Antecedent Biomarkers for AD: The Adult Children Study—Clinical Core

Total Planned Enrollment: 75

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	25	50	75
Ethnic Category: Total of All Subjects *	25	50	75
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	8	12
White	21	42	63
Racial Categories: Total of All Subjects *	25	50	75

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

9. INCLUSION OF CHILDREN
Due to the age-related nature of Alzheimer's disease children age 18 years and younger will not be studied. .

10. VERTEBRATE ANIMALS—Not Applicable

11. SELECT AGENTS— Not Applicable

12. MULTIPLE PD/PI LEADERSHIP PLAN— Not Applicable

13. CONSORTIUM/CONTRACTUAL ARRANGEMENTS— Not Applicable

14. LETTERS OF SUPPORT/CONSULTANTS
Dr. David M. Holtzman, Professor and Chair, Department of Neurology
Dr. R. Gilbert Jost, Professor and Chair, Department of Radiology
Dr. Steven E. Petersen, Director, The McDonnell Center for Systems Neuroscience
Dr. D.C. Rao, Professor and Director, Division of Biostatistics
Dr. Larry J. Shapiro, Executive Vice Chancellor for Medical Affairs and Dean, School of Medicine
Dr. Mark S. Wrighton, Chancellor, Washington University

15. Resource Sharing Plan (s)

Intellectual Property and Data Sharing. The ACS PPG is committed to the sharing of intellectual property and research resources (e.g. tissue and data) with minimum restriction. Intellectual property and data generated from the ACS PPG will be administered in accordance with the policies of Washington University and NIH, including the Bayh-Dole Act of 1980, the NIH Data Sharing Policy and Implementation Guidance of March 5, 2003, the RFA-AG-04-011, and the Health Insurance Portability and Accountability Act (HIPAA).

Inventions: Ownership of sole or joint inventions developed from the ACS PPG will be owned by the institution(s) employing the inventor(s). Inventorship shall be determined by U.S. Patent Law, Title 35, United States Code. University and participating investigators/institutions will disclose any inventions developed under the project and such inventions will be reported and managed as provided by NIH policies. Sole inventions will be administered by the institution employing the inventor. Joint inventions shall be administered based on mutual consultation between the parties. Similar procedures will be followed for copyrights.

Materials: Materials generated from the ACS PPG will be disseminated in accordance with Washington University ACS/HASD/ADRC (see 'Requesting Resources" below) and NIH policies. Depending on such policies, materials will be transferred to others under the terms of a material transfer agreement or simple letter of agreement using the least restrictive language possible.

Data Sharing: Data generated by investigators of the ACS PPG for specific research projects will be published during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. Research data that documents, supports and validates research findings will be made available after the main findings from the final research data set have been accepted for publication. Such research data will be de-identified to prevent the disclosure of personal identifiers.

Data generated by investigators for the ACS PPG central database will be shared with qualified investigators as approved by the Executive Committee according to established policies and procedures (see 'Requesting Resources', below).

Participants in the ACS PPG are informed in their consent documents that data and biological samples collected will be coded to prevent disclosure of protected health information (PHI) and any research health information, in compliance with HIPAA regulations; and these data and biological samples may be shared with other institutions or companies as approved by the Executive Committee. Subjects also relinquish any proprietary interest in the data or specimens they provide in the course of this research.

AD Genetics Data Sharing: Through the Knight ADRC Genetics Core, the ACS PPG will follow NIH guidelines on the sharing of genetic material and associated data as stated in the "POLICY FOR SHARING RESOURCES AND DATA FROM STUDIES ON THE GENETICS OF ALZHEIMER'S DISEASE."

Requesting Resources: If investigators, other than ACS investigators, wish to access data or tissue generated by the ACS PPG, they will follow the procedures and policies established by the Executive Committee. Qualified investigators initiate requests for resources by providing basic information about their research project; the instructions and forms, including a 3 page research summary and NIH biosketch, are web-based for easy access. Prospective investigators are encouraged to consult with appropriate Core and Project leaders and the data manager. In the case of tissue or subjects, written reviews of the request are provided by experts for discussion and approval by the Executive Committee. The criteria used by reviewers are: scientific merit, feasibility and IRB issues, appropriateness of principal investigator qualifications, burden on sample(s) (e.g., tissue resources), burden on staff, and appropriateness to ACS PPG goals/themes. The Executive Committee operates under standard rules of parliamentary procedure when considering requests for resources. After discussion, a request may be approved by a simple majority of the members present and voting.