Overall Specific Aims

The Healthy Aging and Senile Dementia (HASD) Program Project Grant (PPG; P01 AG03991; JC Morris, PI) has been continuously funded since 1984 and seeks funding with this renewal application for Years 36-40 to address critical but as yet unresolved questions about preclinical Alzheimer disease (AD). These questions are: 1) will all cognitively normal (CN) older adults with preclinical AD, defined by the presence of molecular biomarkers of AD, inevitably develop symptomatic AD if they continue to live?; 2) what factors indicate that an individual with preclinical AD is transitioning to symptomatic AD phenoconversion?; 3) what genetic, biological, and non-biological factors confer protection (resilience) that allows individuals with preclinical AD to remain CN?; and 4) are there racial disparities in the molecular biomarkers used to characterize preclinical AD? HASD is ideally poised to address each of these questions in the next funding period due to its many notable strengths, including an established, richly phenotyped, longitudinal cohort of CN older adults that is >18% African American (AA); a long tradition of comprehensive AD molecular biomarker studies that produced our extensive biospecimen repository; novel hypotheses and research strategies; a highly collaborative, productive, and talented investigative team; committed and experienced leadership; and a strongly supportive environment. In this application, HASD introduces new measures and modalities to address the questions noted above. These include a novel enrollment strategy that enriches the cohort with biomarker-positive CN participants, the addition of positron emission tomography (PET) with [18F] AV-1451, a tau radioligand, and of cerebrospinal fluid (CSF) markers of axonal and synaptic injury to permit the correlation of tau burden and distribution and of synaptic dysfunction with the transition to symptomatic AD (proposed Project 1), an examination of the genetic variants that confer resilience (proposed Project 3), and multiple innovative efforts to increase AA participation in AD molecular biomarker studies and evaluate potential racial disparities (proposed Project 1). With additional initiatives to investigate the role of sleep and the orexinergic system in preclinical AD (proposed Project 2) and the introduction of ambulatory measurement burst assessments of cognitive function with the use of a smartphone application (proposed Project 4), HASD in its next budget period will implement the necessary "next steps" to further the understanding of the relationships of preclinical and symptomatic AD.

Overall Specific Aims of this application are to:

1) Continue the well-established, highly productive, and strongly cohesive HASD infrastructure that is organized into the five Cores that support the PPG's scientific initiatives: Core A: Administration, Core B: Clinical, Core C: Biostatistics, Core D: Neuropathology (including its Biofluids Laboratory), and Core E: Imaging
2) Maintain the Core B: Clinical cohort of ~250 participants, age 65 years and older, both those who are CN and those affected by symptomatic AD, by enrolling ~40 new participants (including ~11 AAs) annually
3) At baseline and annually thereafter, provide clinical and cognitive assessments (and obtain smartphone assessments every six months) for all participants, and at baseline and every three years thereafter obtain: a) multiple sleep parameters over a six-day period; b) blood for DNA extraction; c) CSF; and d) brain imaging (magnetic resonance imaging and PET with radioligands for amyloid and tau).
4) Obtain consent for brain autopsy in participants who die
5) Support the new collaboration with the Emory Alzheimer Disease Research Center to currently and prospectively share CSF from all participants, including AAs.
6) Support the completion of the Aims of Projects 1-4 (see Table 1) and promote integrative analyses of all HASD data.

Table 1. Correspondence of Proposed HASD PPG with Current Structure

	Current (8/15/14-4/30/19)	Proposed (5/1/19-4/30/24)
Core	A: Administration (JC Morris)	A: Administration (JC Morris)
	B: Clinical (JC Morris)	B: Clinical (JC Morris)
	C: Biostatistics (C Xiong)	C: Biostatistics (C Xiong)
	D: Neuropathology (R Perrin)	D: Neuropathology (R Perrin)
	E: Imaging (T Benzinger)	E: Imaging (T Benzinger)
Projects	1. Cognitive and functional indicators of transition to symptomatic AD (JC Morris)	1. Characterization of molecular biomarker profiles throughout its pathobiological continuum (JC Morris)
	2. Sleep: Potential prognostic and theranostic marker for preclinical AD (DM Holtzman)	2. Sleep and orexin: potential markers of progression from preclinical to symptomatic AD (B Lucey)
	3. Identification of genetic variants associated with rate of disease progression (C Cruchaga)	3. Dissecting the genetic architecture of resilience (C Cruchaga)
	4. Imaging markers of neuronal dysfunction in preclinical Alzheimer disease (T Benzinger)	4. Smartphone-based "burst" cognitive assessments (J Hassenstab)

Overall Research Strategy

Glossary of terms and abbreviations used in this application

HASD: Healthy Aging and Senile Dementia (P01 AG03991)
ADRC: Alzheimer Disease Research Center (P50 AG05681), endowed by the Knight family in 2010
ACS: Adult Children Study (P01 AG026276)
TR: Total Registry: participants age 65 and older in the HASD, ADRC, ACS grants intentionally are assessed with an identical protocol, and together they represent a combined uniform cohort
AA: African American (self-identified)
NHW: non-Hispanic white (self-identified)
AD: Alzheimer disease, the pathobiological disorder regardless of clinical status
- **Preclinical AD**: the disorder prior to its clinical expression; persons with preclinical AD are cognitively normal (**CN**)
- **Symptomatic AD**: the clinically expressed disorder; the term encompasses mild cognitive impairment (**MCI**) due to AD and **AD dementia**

Aβ: Amyloid-beta peptide
APOE: Apolipoprotein E; the ε4 allele confers increased susceptibility for AD
CDR: Clinical Dementia Rating
CSF: Cerebrospinal fluid, obtained by lumbar puncture (**LP**)
MRI: magnetic resonance imaging (performed at 3 Tesla)
PET: Positron emission tomography
- **PiB:** [11C] Pittsburgh Compound-B, an Aβ radioligand
- **AV-1451**: also known as [18F] flortaucipir and as T807, a tau radioligand

NIH/NIA: National Institutes of Health/National Institute on Aging
PPG: Program Project Grant
CL/PL: Core Leader/Project Leader
PI: Principal Investigator

A. SIGNIFICANCE

The Summary Statement (released 1/4/2014) for the last HASD renewal application noted perceived weaknesses: 1) unclear boundaries of this PPG with other programs at Washington University; 2) lack of HASD-specific meetings; 3) most autopsies are in persons with end-stage disease; 4) limited effort for Leader of Core B: Clinical; 5) use tissue pH to indicate agonal state; and 6) address incidental findings on neuroimaging studies. [Note: critiques of current Project 1 are not presented here as this Project has been extensively revised in this application, and hence the comments that relate, for example, to attentional control measures no longer are germane.] The above weaknesses are addressed here: 1) The HASD, ADRC, and ACS grants by design share common infrastructure, personnel, and other resources regarding participant recruitment and assessment for two major reasons: a) to provide a uniformally assessed cohort (the Total Registry; TR) that is larger than any single grant can support; and b) to efficiently utilize our human and fiscal resources. Each grant is fully compliant with NIH guidelines and policies such that all costs associated with the research participation of an individual enrolled in a particular grant are charged to that grant alone. Moreover, while thematically linked in the pursuit of understanding preclinical AD, each grant clearly differs from the others in their distinct scientific aims. These aims, and the publications that address these aims, set the boundaries for each grant. In this application, the unique productivity for HASD aims is provided in Publications in the Overall Progress Report; other publications that used HASD-derived data to help address ADRC or ACS aims are listed separately. 2) We inaugurated HASD-specific quarterly meetings in February 2017 so that advances in each Project can inform each other; these quarterly meetings will continue in the next budget period. 3) Most autopsies occur in participants with end-stage disease because these individuals are at greatest risk of death; in this reporting period for HASD (8/1/14-11/30/17), 5 CDR 0 autopsies (out of 9 deaths) and 9 CDR 0.5/1 autopsies (out of 17 deaths) have been completed in addition to 21 CDR 2/3 autopsies (out of 22 deaths). 4) The Core B: Clinical Leader (JC Morris) now is joined by new Associate CL, GS Day, and together they will devote 20% effort to the leadership of the Core. 5) Tissue pH now is used to evaluate agonal state in postmortem tissue. 6) Core B: Clinical and Core E: Imaging describe our longstanding protocol that informs participants of incidental imaging findings.

Although approximately one-third of older adults 65 years and older have molecular biomarker evidence of AD pathology and thus are considered to represent preclinical AD,(1) it remains uncertain as to whether each individual with preclinical AD is destined to develop symptomatic (if they survive to age at onset). The duration of preclinical AD, from initial development of pathology to symptomatic onset, the pathobiological sequence of

events that culminate in symptoms, and what factors may accelerate or mitigate that process also are all unknown.

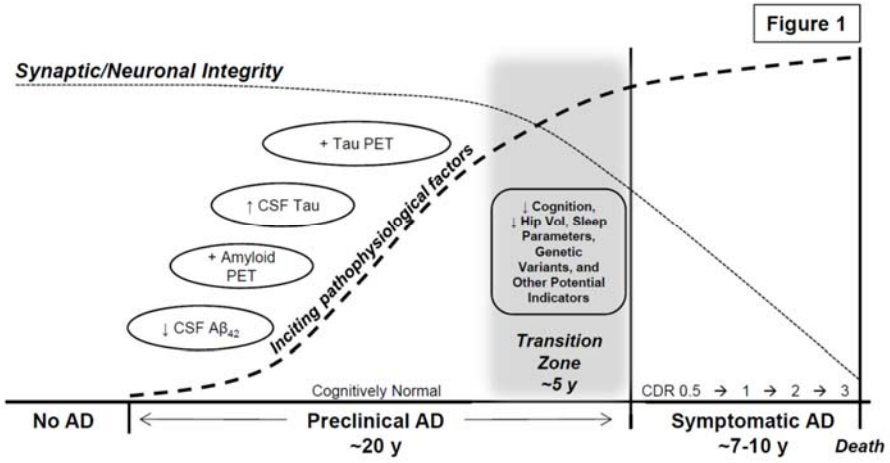
The compelling **Significance** of this application is its exploration of the pathobiological continuum of preclinical AD with a particular emphasis on the factors that are critical for the phenoconversion from asymptomatic to symptomatic AD. In this application, the pursuit of these research aims additionally is framed within the context of identifying potential differences in the molecular biomarkers of AD between African Americans (AA) and non-Hispanic whites (NHWs). Racial differences may suggest new mechanisms that are responsible for AD or, alternatively, indicate that shared mechanisms operate differentially. This application proposes 4 Projects: Project 1 (JC Morris, PL), "Characterization of molecular biomarker profiles throughout its pathobiological continuum", will evaluate factors, including the amount and topographical "spread" of tau pathology as imaged by tau PET, that may be critical for the phenoconversion from asymptomatic to symptomatic AD and also will characterize potential racial disparities in the molecular biomarkers of AD; Project 2 (B Lucey, PL), "Sleep and orexin: potential markers of progression from preclinical to symptomatic AD", will assess changes in sleep parameters and in the orexinergic system as contributors to phenoconversion; Project 3 (C Cruchaga, PL), "Dissecting the genetic architecture of resilience" will examine genetic variants in individuals who remain CN despite having the molecular biomarkers of AD; and Project 4 (J Hassenstab, PL), "Smartphone-based burst cognitive assessments", will administer cognitive evaluations in the participant's usual environment using a measurement burst design via a smartphone application. These four Projects are supported by five Cores: Core A: Administration (JC Morris, CL), Core B: Clinical (JC Morris, CL), Core C: Biostatistics (C Xiong, CL), Core D: Neuropathology (R Perrin, CL), and Core E: Imaging (T Benzinger, CL). The organizational structure for this application is shown in Table 1 in the Specific Aims.

The research agenda for HASD in this application is of critical importance to the field, particularly as an increasing number of clinical trials of investigational anti-AD agents have launched for CN older adults with preclinical AD(2) in an effort to delay or even prevent the symptomatic onset of AD. HASD's research agenda also is ambitious. For example, we propose to obtain longitudinal molecular biomarkers, including amyloid PET, tau PET, and CSF for assays of $A\beta_{42}$, t-tau, p-tau_{181}, and other analytes, from all participants, including a sizeable number of AAs. Although completing our research agenda will be a major undertaking, HASD will leverage its well-established strengths to accomplish its goals.

A particular strength of HASD since its initial funding in 1984 has been its leadership, beginning with its founding PI, Leonard Berg, MD. Dr. Berg transitioned the leadership of the PPG to his mentee, JC Morris, beginning with the HASD renewal application submitted in June 1997. Morris has recruited an exceptionally strong and stable group of investigators to the HASD team. In the current HASD budget period, David Holtzman, MD, Jones Professor and Chair of Neurology, serves as Associate Program Director and Krista Moulder, PhD, serves as Executive Director; both continue their roles in this application. Chengjie Xiong, PhD, became Leader of Core B: Biostatistics in 2008 as an Assistant Professor after he completed his K25 Mentored Quantitative Research Career Award with Morris as his mentor; Tammie Benzinger, MD, PhD, became Leader of Core E: Imaging in 2010 as an Assistant Professor. Xiong and Benzinger continue their roles in this application and are examples of how HASD provides early-stage investigators with research and leadership opportunities that have been instrumental in advancing their careers. In this application, other early-stage individuals now assume leadership roles. Dr. Gregory Day, Assistant Professor of Neurology, completed his postdoctoral fellowship with Morris in 2016 and now becomes Associate CL of Core B: Clinical . Rick Perrin, MD, PhD, Assistant Professor of Pathology (Neuropathology) and Immunology, initially was the Associate CL for Core D: Neuropathology in the current budget period and was appointed CL on 12/1/17 when Nigel Cairns, PhD, announced his retirement, effective 8/1/18 (Dr. Cairns graciously is assisting Dr. Perrin as he transitions into the Core leadership responsibilities). Brendan Lucey, MD, Assistant Professor of Neurology and Director of the Sleep Medicine Section in the Department of Neurology, is co-investigator for current Project 2 and will serve as Project 2 Leader in the next budget period. Jason Hassenstab, PhD, was recruited to Washington University by Morris in 2010 to work on the cognitive component of HASD with one of HASD's founders, Martha Storandt, PhD, prior to her retirement in 2012. Dr. Morris served as Dr. Hassenstab's mentor for his K23 mentored Patient-Oriented Research Career Development Award (2012-2017). Dr. Hassenstab is adapting modern technology to support user-friendly, repeatable cognitive assessments with a smartphone application that administers measurement "bursts" in proposed Project 4 (J. Hassenstab PL). Carlos Cruchaga, PhD, was Assistant Professor of Psychiatry and Co-Project Leader (with Alison Goate, PhD) when current Project 3 began in 2014; he now is Associate Professor and is sole Leader of proposed Project 3. With the support of Morris and the HASD, these leadership developments reflect the growth of the "next generation" of superb HASD investigators. Morris also has pledged to promote diversity among program faculty. To that end, he recently recruited Lenise Cummings-Vaughn, MD, an African American Assistant Professor of

Medicine (Geriatrics), to the physician team providing assessments in Core B: Clinical (Dr. Cummings-Vaughn is sourced from HASD in the current budget period).

Dr. Morris as PI has successfully guided HASD through four funding cycles. He is deeply committed to the scientific investigations supported by HASD, both current and proposed, as he was instrumental in developing HASD's concept of preclinical AD (see Figure 1).(3-5) Under his leadership, HASD supported the first *in vivo* demonstration of preclinical AD in CN older adults and was the first program to show that preclinical AD is associated with substantially greater risk of symptomatic AD.(6-8) To capitalize on the wealth of highly capable leaders associated with the AD program at Washington University, Morris transitioned the leadership of the Dominantly Inherited Alzheimer Network (DIAN; UF1 AG032438, for which Morris was the founding PI), to Randall Bateman, MD (another Morris mentee), in 2015 and will transition the leadership of the ADRC grant (P50 AG05681) to Dr. Holtzman when departmental responsibilities permit within the next budget period of the ADRC. Due to his longstanding commitment to the scientific aims of HASD, Morris remains as its PI (and also as PI for its closely linked PPG, the ACS P01 AG026276). At the same time, Morris is establishing succession planning (e.g., Holtzman as Associate Program Director for HASD, Day as Associate Leader of HASD's Core B: Clinical).



Each HASD PL and CL is highly accomplished; all have worked productively with Dr. Morris and with each other for years. The hallmarks of HASD that result in the whole continuing to be far greater than the sum of its parts include a multidisciplinary, collaborative investigative team, a highly integrated and cohesive organization, the supportive environment that enables the career development of early-stage investigators, and a strong track record of productivity, as measured both by publication record and ability to leverage resources to support successful applications for externally-funded research. For example, in the current budget period HASD was awarded a competing revision (TL Benzinger, PL) that introduced tau PET to our biomarker studies. In the reporting period of 8/1/14-11/30/17, HASD investigators have generated an additional ~$41 million (total costs) in other new AD-related grants; (see Core A: Administration). The strengths of HASD all are manifest in this renewal application and together ensure that HASD will accomplish its aims.

B. INNOVATION

This HASD renewal application, to our knowledge, proposes the first longitudinal and multimodal investigation of molecular biomarkers of AD that examine possible racial disparities (Project 1). To provide adequate power to address these possible disparities, Project 1 will implement novel strategies to increase the numbers and participation rates of AAs in molecular biomarker research. These strategies include a collaboration with the Emory University ADRC to share biofluids (CSF; blood/plasma) from AA and NHW participants, using specimens already collected as well as future specimens. Other innovative aspects of this application include the scientific aims in Projects 1-4, including the inclusion of tau PET imaging and of CSF markers of axonal and synaptic injury to characterize the transition from asymptomatic to symptomatic AD and a recruitment strategy in Core B: Clinical that enriches the CN cohort with individuals with preclinical AD. Dr. Hassenstab and colleagues have secured an open access license through Washington University to permit research use of the novel smartphone application for ambulatory cognitive assessments without costs, contractual obligations, or intellectual property concerns. This open access policy for the smartphone application complements the sharing of source (DICOM) imaging from 691 HASD participants in its 2018 public data release through the Open Access Series of Imaging Studies-3 (OASIS-3); www.oasis_brains.org) (see Core E: Imaging). OASIS originally was developed and launched by HASD's Imaging Core in 2007 with cross-sectional data(9) and subsequent longitudinal imaging data.(10)

C. APPROACH

C.1. Progress Report (8/1/14-11/30/17)

In this application, Projects 2 and 3 are extensions of current Projects 2 and 3 and hence their Progress is reported in their respective Research Strategy sections as is the Progress of each Core. Progress in current Project 4 (the competing revision) also is reported in the Research Strategy Section of Core E: Imaging.

Project 1 in this application, however, is notably different from current Project 1 as the proposed Project 1 no longer has Aims that address attentional control measures or disruptions in resting state networks. New Project 1 instead incorporates new biomarker modalities, including tau PET imaging (from current Project 4) and CSF analytes of axonal and synaptic injury, to characterize the phenoconversion from asymptomatic to symptomatic AD; our preliminary data (see proposed Project 1 in this application) indicate that AAs have significantly **lower** CSF levels of tau than NHWs and have a **lower** cumulative incidence of symptomatic AD. It also adds a novel Aim to explore racial disparities in molecular biomarkers of AD. Progress for current Project 1 is provided here. (Proposed Project 4 does not have a counterpart in the current budget period and thus has no progress to report.)

C.1.1. Project 1

a. Absence of practice effects in preclinical AD: Annual cognitive assessments of 263 CN older adults for a mean of 9.5 visits found that 197 (75%) remained CN (stable) but that 66 (25%) developed symptomatic AD (progressors). The stable group experienced a performance gain in episodic memory performance over the first three annual assessment that was absent for the progressors. A one unit increase in the estimated annual slope on the episodic memory measure from baseline to third assessment was associated with an 89% reduction in risk for symptomatic AD.(11)

b. Measures of attentional control and semantic memory: Measures of attentional control and semantic memory discriminate CN older adults from those with symptomatic AD and their influence correlates with molecular biomarkers of AD (PiB PET; CSF $A\beta_{42}$; CSF t-tau). CSF $A\beta_{42}$ and CSF t-tau each account for unique variance in the cognitive measures, consistent with earlier work(12) indicating that these biomarkers have independent interactions.(13)

c. Age-related disruptions in functional connectivity: Resting state functional connectivity studies in 297 CN older adults demonstrated that disruptions in the default mode and salience networks strongly correlated with the presence of abnormal CSF $A\beta_{42}$ and t-tau levels. This suggests that reported age-related disruptions in these networks results from preclinical AD.(14)

C.2. Productivity

The current reporting period has produced 119 publications to date that report work specific to HASD's research aims (see Overall Publications). In the same reporting period, 104 additional publications have used HASD resources but were not directly related to HASD aims. There also were 114 publications (of which we are aware) using data from our Open Access Series of Imaging Studies. As discussed in Core A: Administration, HASD in this reporting period was leveraged to add current Project 4 as a competing revision and also to generate an additional ~$41 million in total costs for other newly funded grant applications. Summaries of selected publications illustrate HASD's emphasis on fulfilling the aims that address molecular biomarkers of AD and also underscore its collaborative approach.

C.2.1. The stability of CSF $A\beta_{42}$, tau, and p-tau_{181} as assessed on the INNOTEST assay over a 13 year period revealed an upward drift of ~30% per year in $A\beta_{42}$ measurements, such that recent CSF $A\beta_{42}$ values were 30% higher than values from the same sample assayed a decade or so earlier. These results were confirmed using independent data from the Vrijie University Medical Center (VUMC) in Amsterdam, The Netherlands.(15) Such drift can reduce statistical power and confound analyses.

C.2.2. Studies of new CSF analytes as molecular biomarkers of AD in the current budget period justify the incorporation of these analytes in this renewal application.

a. In collaboration again with our VUMC colleagues in The Netherlands, the diagnostic and prognostic utility of the postsynaptic protein, neurogranin (Ng), was examined in 163 individuals with CSF samples about two years apart. Baseline Ng levels correlated with CSF t-tau and p-tau_{181} but not with CSF $A\beta_{42}$. Individuals with symptomatic AD had elevated CSF Ng levels compared with CN persons, but within-person CSF Ng levels increased only in CN older adults. These findings suggest that Ng may reflect synaptic injury or loss prior to symptomatic onset.(16)

b. The most abundant Aβ isoform, $A\beta_{1-40}$, may be used in a ratio with $A\beta_{42}$ ($A\beta_{42/40}$) to control for inter-individual differences in overall levels of CSF Aβ (e.g., some individuals may have lower CSF Aβ levels that are independent of Aβ being aggregated into plaques). The CSF $A\beta_{42/40}$ ratio showed significantly better concordance with cortical amyloid burden as determined by PiB PET when compared with CSF $A\beta_{42}$ alone.(17)

C.2.3. Molecular biomarkers in preclinical AD

a. Individuals who were CN (N=164) with baseline PiB PET and CSF assays and had at least one follow-up PiB PET included 21 who were PiB-positive at baseline, an additional 20 persons became PIB-positive at the follow-up PET scan ("converters"). At baseline, CSF $A\beta_{42}$ levels in the converter group were significantly lower than levels in the individuals who remained PIB-negative, suggesting that changes in CSF $A\beta_{42}$ and cortical PIB retention are coupled at the earliest stage of preclinical AD.(18)

b. Concomitant florbetapir PET and AV-1451 PET in 36 CN and 10 mildly symptomatic AD participants were used for multivariate analyses that identified stereotypical spatial patterns, or topographies, for Aβ and tau deposition. Tau deposition in the temporal lobe correlated with CSF t-tau levels and was a better predictor of cognitive status than Aβ deposition in any brain region. Tau pathology tracks brain changes that are responsible for early symptomatic AD.(19)

C.2.4. Whole-exome sequencing: A rare variant in phospholipase D_3 (*PLD3*) segregated with symptomatic AD in two independent families with late-onset AD (LOAD). Both genetic and functional data (knockdown of *PLD3* in cell models results in increased extracellular $A\beta_{40}$ and $A\beta_{42}$) suggest that the *PLD3* coding variant confers a two-fold risk for AD.(20)

C.2.5. LOAD caused by a single gene mutation: Using extreme CSF levels of CSF $A\beta_{42}$ as an endophenotype,(21) 10 *PSEN1 A79V* mutation carriers were identified in multiple generations of a family previously considered to have "sporadic" LOAD. The mean age at onset of symptomatic AD was 75 years (range: 63-77 years). The clinical attributes of symptomatic AD in this family were comparable to those of LOAD, providing indirect support to the idea that LOAD and autosomal dominant AD may have overlapping etiologies.(22)

C.3. Experimental Design

The centerpiece of HASD is its clinical cohort of research participants who are 65 years or older and at time of enrollment are all eligible for and agree in principle for our biomarker protocol including brain MRI, PiB PET, AV-1451 PET, and lumbar puncture (LP) to obtain CSF. Clinical and cognitive assessments, based on the Uniform Data Set(23, 24) and supplemented with HASD-specific measures, are conducted at baseline and annually thereafter. Imaging and fluid (CSF; blood) biomarkers are obtained at baseline and every three years thereafter. [Note: AA participants are exempted from the expectation for LP due to its deleterious effect on AA recruitment.] Participants at baseline are either CN (Clinical Dementia Rating [CDR] 0) or have very mild symptomatic AD (CDR 0.5). Symptomatic AD participants are followed with annual in-person assessments until they progress to CDR 2.

There are 237 currently active HASD participants; as noted in **A. Significance** (and in Core A: Administration and in Core B: Clinical), HASD participants are assessed and followed with the identical protocol that is used for participants age 65 years and older who are enrolled in our affiliated ADRC and ACS grants. The Total Registry (TR) of 65 years and older participants has 640 participants (237 from HASD, 257 from ADRC, and 146 from ACS, more than sufficient to address the Aims of Projects 1-4. The 237 HASD participants include 178 (75%) CN individuals and 59 (25%) CDR 0.5/1 individuals; 48 (20%) of the 237 participants are AA. The characteristics for both the HASD and TR cohorts are presented in Core B: Clinical.

The cohort is remarkably committed to participation in HASD. Our retention rate exceeds the mean rate for the 31 Alzheimer Disease Centers (ADCs) as reported to the National Alzheimer's Coordinating Center (NACC) (see Figure 1, Core B: Clinical); our voluntary autopsy rate of 73% exceeds that for all ADCs (58%) although three-fourths of our participants are CN (most successful autopsy rates are driven largely by persons with end-stage AD). Our TR completion rates are 76% for amyloid PET and 77% for LP in NHWs; in AAs, the completion rates are 58% for amyloid PET and 39% for LP.

All Projects in this application will address their Specific Aims with three groups of participants: 1) CN and molecular biomarker-negative (CN-Neg); 2) CN and molecular biomarker-positive (CN-pos, denoting preclinical AD); and 3) cognitively impaired (CDR>0). The large majority of CDR>0 individuals are clinically diagnosed with symptomatic AD. Of 27 autopsies in this reporting period in participants with a clinical diagnoses of AD, with or without comorbid disorders, AD neuropathologic change(25) was present in 26 for a 96% clinical accuracy rate. Table 2 below lists the variables that are available to address Project-specific Aims as each Project compares these three groups of participants.

C.4. Coherence and Inter-relationships

Core A: Administration and Core C: Biostatistics have interacted regularly since February, 2017, with each HASD Project and Core in the planning and preparation of this application. Each Project pursues Project-specific Aims but also combines Project-specific data with other data from all Projects and Cores to address the central themes of HASD. Initially funded in 1984, HASD is the progenitor of all major funded AD research at Washington University and interacts collaboratively and productively with these programs, including the Knight ADRC and the ACS.

HASD enjoys remarkable institutional support from Washington University (see Letters of Support from Chancellor Wrighton, Dean Perlmutter, and Neurology Chair Holtzman). This support takes many facets, including the current office renovation by the School of Medicine for Associate Clinical Core Leader, Dr. Day, and expendable funds annually for our research from the Dean's Office and the McDonnell Center for Systems

Neuroscience. A key aspect of the institutional support is the University's commitment to enabling the philanthropy directed to Dr. Morris that in turn is used to support HASD (see Core A: Administration).

C.5. Rigor and Reproducibility

HASD investigators work on many levels to ensure scientific rigor and reproducibility in our experimental strategy, methods, and analyses. The experimental design for each Project was designed in close consultation with Core C: Biostatistics, as were the analytic plans. Sex, race, education, and *APOE* genotype are accounted for as appropriate in all analyses. Each HASD Core generates and adheres to standard operating procedures (e.g., uniform protocols for neuropathological assessment by Core D: Neuropathology; common processing pipelines for Core E: Imaging) for ascertainment of Core data. Biological and chemical resources that could be subject to variability have quality-control standards (Core D: Neuropathology, Core E: Imaging, and Project 3).

Table 2. Partial List of HASD Variables

Clinical	Cognitive	Other
Demographics Age Sex Education Race (white, AA, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, Asian, other) Hispanic/Latino ethnicity Marital status Family history of dementia (1st degree relative) Living Situation Hollingshead Index of Social Position **Health conditions/medical diagnosis** Stroke Diabetes (Type I, Type II) Hypertension Hypercholesterolemia Heart disease (myocardial infarction, CHF, coronary intervention) Thyroid disease B_{12} deficiency Falls Cancer Substance abuse (including frequency of alcohol use) Tobacco use (pack-year history) Sleep disorders Medications **Affective/psychiatric disorders** Neuropsychiatric Inventory Geriatric Depression Scale Clinician's assessment of depressive features **Examination** Height and weight to derive body mass index Seated blood pressure, pulse Visual acuity HbA1c Neurological examination **Cognitive/functional measures** Autobiographical recall(26) Aphasia battery Short Blessed Test Functional Assessment Scale Clinical Dementia Rating (global CDR) CDR-SumBox Clinician diagnosis of cognitive disorder	**UDS 3 Psychometric Tests** Montreal Cognitive Assessment (MoCA) Craft Story 21 Recall, Immediate and Delayed Benson Complex Figure: Copy, Recall and Recognition Number Span Test: Forward & Backwards Category Fluency (Animals, Vegetables) Trailmaking A and B Multilingual Naming Test (MINT) Verbal Fluency for Letters F & L **Additional HASD Longitudinal Psychometric Tests** Mini Mental State Examination (MMSE) Wechsler Memory Scale: Associate Learning & Mental Control Wechsler Adult Intelligence Scale: Block Design & Information Wechsler Adult Intelligence Scale – Revised: Digit Symbol Substitution Wechsler Adult Intelligence Scale III: Letter Number Sequencing Free and Cued Selective Reminding Test Switching Task (consonant vowel odd and even) Simon Task Stroop Color Only Task Stroop Switch Tapping Task Handedness – (At entry only) Literacy (Slosson Oral Reading Test – Revised) – (At entry only)	**Genetic Data** *APOE* GWAS Exome-chip **Imaging** Brain MRI Hippocampal volume Cortical thickness WMHs Infarcts Microhemorrhages Indiv. Longitudinal Participant volumetric report PiB PET BPs SUVR Centiloids AV-1451 PET BPs SUVR Centiloids Tau spatial spread Tau index summary region variable **CSF** Aβ42 Aβ40 t-tau p-tau_{181} NfL Ng SNAP-25 **Sleep Parameters** NREM slow wave activity Time in each sleep stage (Wake, NREM stage 1/2/3, REM) Sleep Efficiency Total sleep time Sleep latency

Overall Bibliography and References Cited

1. Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA. APOE predicts Ab but not tau Alzheimer's pathology in cognitively normal aging. Ann Neurol. 2010;67:122-31.
2. Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, Aisen PS. The A4 Study: Stopping AD before symptoms begin? Sci Trans Med. 2014;228:1-3.
3. Morris JC, McKeel DW, Jr., Storandt M, Rubin EH, Price JL, Grant EA, Ball MJ, Berg L. Very mild Alzheimer's disease: Informant-based clinical, psychometric, and pathological distinction from normal aging. Neurology. 1991;41:469-78.
4. Morris JC, Storandt M, McKeel DW, Rubin EH, Price JL, Grant EA, Berg L. Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. Neurology. 1996;46(3):707-19. PubMed PMID: WOS:A1996UB77800022.
5. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol. 1999;45(3):358-68. Epub 1999/03/11. PubMed PMID: 10072051.
6. Fagan AM, Roe CM, Xiong C, Morris JC, Holtzman DM. Cerebrospinal fluid tau/ß-amyloid$_{42}$ ratio as a prediction of cognitive decline in nondemented older adults. Arch Neurol. 2007;64(3):343-9.
7. Morris JC, Roe CM, Grant EA, Head D, Storandt M, Goate AM, Fagan AM, Holtzman DM, Mintun MA. Pittsburgh Compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer's disease. Arch Neurol. 2009;66:1469-75.
8. Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, Cairns NJ, Morris JC, Holtzman DM, Fagan AM. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol. 2013;12(10):957-65. Epub 2013/09/10. doi: 10.1016/S1474-4422(13)70194-7. PubMed PMID: 24012374; PMCID: PMC3904678.
9. Marcus DS, Wang TH, Parker J, Csernansky JG, Morris JC, Buckner RL. Open Access Series of Imaging Studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. J Cogn Neurosci. 2007;19(9):1498-507. Epub 2007/08/24. doi: 10.1162/jocn.2007.19.9.1498. PubMed PMID: 17714011.
10. Marcus DS, Fotenos AF, Csernansky JG, Morris JC, Buckner RL. Open access series of imaging studies: longitudinal MRI data in nondemented and demented older adults. J Cogn Neurosci. 2010;22(12):2677-84. Epub 2009/11/26. doi: 10.1162/jocn.2009.21407. PubMed PMID: 19929323; PMCID: PMC2895005.
11. Hassenstab J, Ruvolo D, Jasielec M, Xiong C, Grant E, Morris JC. Absence of practice effects in preclinical Alzheimer's disease. Neuropsychology. 2015;29(6):940-8. Epub 2015/05/27. doi: 10.1037/neu0000208. PubMed PMID: 26011114; PMCID: PMC4640964.
12. Storandt M, Head D, Fagan AM, Holtzman DM, Morris JC. Toward a multifactorial model of Alzheimer disease. Neurobiol Aging. 2012;33(10):2262-71. Epub 2012/01/21. doi: 10.1016/j.neurobiolaging.2011.11.029. PubMed PMID: 22261556; PMCID: PMC3334456.
13. Aschenbrenner AJ, Balota DA, Tse CS, Fagan AM, Holtzman DM, Benzinger TL, Morris JC. Alzheimer disease biomarkers, attentional control, and semantic memory retrieval: Synergistic and mediational effects of biomarkers on a sensitive cognitive measure Neuropsychology. 2015;29(3):368-81. Epub 2014/09/16. doi: 10.1037/neu0000133. PubMed PMID: 25222200; PMCID: PMC4362851.
14. Brier MR, Thomas JB, Snyder AZ, Wang L, Fagan AM, Benzinger T, Morris JC, Ances BM. Unrecognized preclinical Alzheimer disease confounds rs-fcMRI studies of normal aging. Neurology. 2014;83(18):1613-9. Epub 2014/09/28. doi: 10.1212/WNL.0000000000000939. PubMed PMID: 25261500; PMCID: PMC4223085.
15. Schindler SE, Sutphen CL, Teunissen CE, McCue L, Morris JC, Holtzman DM, Mulder SD, Scheltens P, Xiong C, Fagan AM. Upward drift in cerebrospinal fluid amyloid B42 assay values for more than 10 years. Alzheimer's & Dementia. 2018;14:62-70. Epub 2017 Jul 12; PMCID: PMID:28710906.
16. Kester MI, Teunissen CE, Crimmins DL, Herries EM, Ladenson JH, Scheltens P, van der Flier WM, Morris JC, Holtzman DM, Fagan AM. Neurogranin as a Cerebrospinal Fluid Biomarker for Synaptic Loss in Symptomatic Alzheimer Disease. JAMA Neurol. 2015;72(11):1275-80. Epub 2015/09/15. doi: 10.1001/jamaneurol.2015.1867. PubMed PMID: 26366630; PMCID: PMC4694558.
17. Lewczuk P, Matzen A, Blennow K, Parnetti L, Molinuevo JL, Eusebi P, Kornhuber J, Morris JC, Fagan AM. Cerebrospinal fluid AB42/40 corresponds better than AB42 to amyloid PET in Alzheimer's disease. J Alzheimers Dis. 2017;55:813-922; PMCID: PMC5147502.

18. Vlassenko AG, McCue L, Jasielec MS, Su Y, Gordon BA, Xiong C, Holtzman DM, Benzinger TL, Morris JC, Fagan AM. Imaging and cerebrospinal fluid biomarkers in early preclinical alzheimer disease. Ann Neurol. 2016;80(3):379-87. Epub 2016/07/12. doi: 10.1002/ana.24719. PubMed PMID: 27398953; PMCID: PMC5016232.
19. Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Owen C, Aldea P, Su Y, Hassenstab J, Cairns NJ, Holtzman DM, Fagan AM, Morris JC, Benzinger TLS, Ances BM. Tau and AB imaging, CSF measures, and cognition in Alzheimer's disease. Sci Trans Med. 2016;8:338ra66; PMCID: PMC5267531.
20. Cruchaga C, Benitez B, Karch CM, Harari O, Norton J, Jeng AT, Cooper B, Jin SC, Cai Y, Skorupa T, Carrell D, Levitch D, Guerreiro R, Ryten M, Sassi C, Bras J, Gibbs JR, Hernandez DG, Lupton MK, Powell J, Forabosco P, Ridge PG, Corcoran CD, Tschanz JT, Norton MC, Munger RG, Schmutz C, Leary M, Demirci TF, Bamne MN, Wang X, Lopez O, Ganguli M, Medway C, Turton J, Lord J, Braae A, Barber I, Brown K, Consortium TAsRUA, Pastor P, Lorenzo O, Brkanac Z, Scott E, Topol E, Kauwe JSK, Morgan K, Rogaeva E, Singleton A, Hardy J, Kamboh IM, St.George-Hyslop P, Cairns N, Morris JC, Goate AM. Rare coding variants in Phospholipase D3 (PLD3) confer risk for Alzheimer's disease. Nature. 2014;505:550-4; PMCID: PMC4050701.
21. Kauwe JS, Jacquart S, Chakraverty S, Wang J, Mayo K, Fagan AM, Holtzman DM, Morris JC, Goate AM. Extreme cerebrospinal fluid amyloid beta levels identify family with late-onset Alzheimer's disease presenilin 1 mutation. Ann Neurol. 2007;61(5):446-53. Epub 2007/03/17. doi: 10.1002/ana.21099. PubMed PMID: 17366635.
22. Day GS, Musiek ES, Roe CM, Norton J, Goate AM, Cruchaga C, Cairns NJ, Morris JC. Phenotypic Similarities Between Late-Onset Autosomal Dominant and Sporadic Alzheimer Disease A Single-Family Case-Control Study. Jama Neurology. 2016;73(9):1125-32. doi: 10.1001/jamaneurol.2016.1236. PubMed PMID: WOS:000384205200015; PMCID: PMC5025942.
23. Morris JC, Weintraub S, Chui HC, Cummings J, Decarli C, Ferris S, Foster NL, Galasko D, Graff-Radford N, Peskind ER, Beekly D, Ramos EM, Kukull WA. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006;20(4):210-6. Epub 2006/11/30. doi: 10.1097/01.wad.0000213865.09806.92. PubMed PMID: 17132964.
24. Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, Dietrich W, Beekly D, Kukull W, Morris JC. The Alzheimer's Disease Centers' Uniform Data Set (UDS): The Neuropsychological Test Battery. Alz Dis Assoc Disord. 2009;23:91-101; PMCID: PMC2743984.
25. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT, National Institute on A, Alzheimer's A. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012;123(1):1-11. Epub 2011/11/22. doi: 10.1007/s00401-011-0910-3. PubMed PMID: 22101365; PMCID: PMC3268003.
26. Dreyfus DM, Roe CM, Morris JC. Autobiographical memory task in assessing dementia. Arch Neurol. 2010;67(7):862-6. Epub 2010/07/14. doi: 10.1001/archneurol.2010.145. PubMed PMID: 20625094; PMCID: PMC2904638.