Overall Specific Aims

The overarching goal of the Knight Alzheimer Disease Research Center (ADRC) is to foster and facilitate innovative and impactful research in Alzheimer disease (AD) and related dementias (ADRD) that ultimately provides the scientific understanding to enable the development of truly effective therapies for these disorders. The Knight ADRC's efforts thus fully align with the primary goal of the National Alzheimer's Project Act of 2011, "to prevent and effectively treat ADRD by 2025". This application proposes to provide well-developed services (including recruitment strategies that ensure the diversity of our research participants), exceptional resources (including a deeply phenotyped clinical cohort and their data and biospecimens), and broad-based transdisciplinary expertise to support and advance studies that address the etiology, pathogenesis, diagnosis, molecular profiling, treatment, and prevention of ADRD. In particular, we focus on the multimodal molecular biomarker characterization of preclinical AD to accelerate knowledge of this asymptomatic stage that will ultimately allow optimized design of prevention trials that aim to delay or even avert the onset of dementia. The following Specific Aims describe our plans to achieve these goals.

1. Coordinate, integrate, and support the transdisciplinary Knight ADRC clinical, translational, and biomedical investigators in their cutting-edge ADRD research.
2. Provide these investigators with exceptionally well-characterized, longitudinally followed research participants, both cognitively normal and those with symptomatic AD (this term encompasses participants with mild cognitive impairment [MCI] due to AD and with AD dementia).
   A. Assure that the participants reflect the racial diversity of the greater St. Louis metropolitan area.
   B. Obtain in participants at baseline and annually thereafter standard clinical, behavioral, and cognitive data, with instruments that include the Uniform Data Set (UDS), and transmit UDS data to the National Alzheimer's Coordinating Center (NACC).
   C. Through affiliated grants, obtain at baseline and longitudinally (every three years) brain MRI, resting state functional MRI (rs fcMRI), amyloid and tau PET scans, and biofluids (blood; cerebrospinal fluid) to support the genetic and biomarker studies of the Knight ADRC.
   D. Refer selected participants to the Genetics and High Throughput -Omics Core for skin biopsy to support the new Knight ADRC Biomarker Core and its studies of induced pluripotent stem cells (iPSCs).
   E. Obtain consent from participants for brain autopsy to support the Knight ADRC's Neuropathology Core.
3. Provide a rich training environment, as implemented by the Knight ADRC's new Research Education Component (REC), for students, fellows, and junior faculty, support their successful career development in ADRD research, and encourage early-stage investigators to apply for Developmental Project funding.
4. Work with other national AD programs (e.g., ADCs, NACC; ADNI; NCRAD; ACTC; GAP; ADGC) and stakeholders (e.g., Alzheimer's Association) to promote collaborative research in ADRD
5. Maintain the coherence, productivity, and centeredness of the Knight ADRC as organized into the six mandatory Cores, an additional Genetics and High Throughput -Omics Core, and the REC (see Figure 1).
6. Address Research Implementation Milestones as shown in Table 1.

Figure 1: Knight ADRC 2020-2025

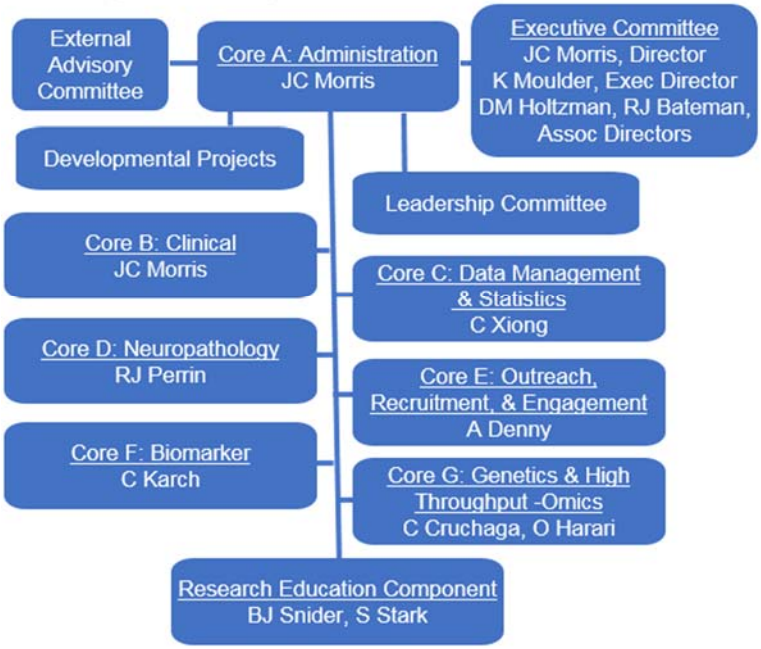


Table 1: AD/ADRD Research Implementation Milestones (M) Addressed by each Core	
Admin:	M.9.B; M.9.G; M16.A.4; M3.C; M4.D; M12.A; M3.A; M.3D
Clin:	M9.H; M1.A; M19.C.4;M11.C; M2.D; M2.J; M2.F; M22.A.1; M2.H
DMS:	M3.C; M3.A.
NPC:	M22.A.1; M22.B.2; M3.D
ORE:	M12.H; M19.D.7; M16A.3
Biomarker:	M21.A.2; M21.A.4; M4.F; M2.G
Genetics:	M9.B; M21.A.2; M4.K; M4.L; M.2G
REC:	M4.J

Overall Research Strategy

Glossary of abbreviations and terms used in this application

ADRC-centric Programs at Washington University (WU) and its School of Medicine (WUSM)

ADRC: Alzheimer Disease Research Center (P50 AG05681; JC Morris, PI); endowed in 2010 by Charles F. and Joanne Knight (**Knight ADRC**)

PPGs: Program Project Grants; the Knight ADRC provides intellectual, infrastructure, and philanthropic support for two biomarker-centric PPGs, **HASD**: Healthy Aging and Senile Dementia (P01 AG03991; JC Morris, PI) and **ACS**: Antecedent Biomarkers for AD: The Adult Children Study (P01 AG026276; JC Morris, PI)

DIAN: Dominantly Inherited Alzheimer Network (UF1 AG032438; RJ Bateman, PI); the **Trial Unit** (**TU**) for DIAN is funded via multiple sources to conduct clinical trials and represents a public-private partnership.

MAP: The Memory and Aging Project, the clinical research office conducting the clinical and cognitive assessments for participants at WU who are enrolled in the ADRC, HASD, ACS, DIAN, and DIAN-TU studies.

Multicenter Collaborative Grants

ACTC: Alzheimer Clinical Trials Consortium (U24 AG057437; P Aisen, R Petersen, R Sperling, PIs)

ADNI: Alzheimer Disease Neuroimaging Initiative (U19 AG024904; MW Weiner, PI); ADNI's Neuropathology Core is at WU (JC Morris, Core Leader)

GAP: Global Alzheimer Platform

NCRAD: National Centralized Repository for Alzheimer Disease and Related Disorders (U24 AG021886; T. Foroud, PI), to which the Knight ADRC sends participant biospecimens

NACC: National Alzheimer Coordinating Center (U01 AG016976; W Kukull, PI), the data repository for all National Institute on Aging (**NIA**)-funded Alzheimer Disease Centers (**ADCs**)

ADGC: Alzheimer Disease Genetics Consortium (U01 AG032984; GD Schellenberg, PI)

Definitions

AD: Alzheimer disease, the brain disorder regardless of clinical status

Preclinical AD: asymptomatic AD, identified with molecular biomarkers for AD; individuals with preclinical AD are cognitively normal (**CN**)

Symptomatic AD: Clinically expressed AD, with symptom severity ranging from very mild (prodromal AD; mild cognitive impairment (**MCI**) due to AD) to severe

Aβ: Amyloid-beta protein, generated by cleavage of the amyloid precursor protein (**APP**)

APOE*/APOE**: the gene and protein, apolipoprotein E; the ***ε4 allele confers susceptibility for AD

CL: Core Leader

DMS: Data Management and Statistics Core

NPC: Neuropathology Core

ORE: Outreach, Recruitment, and Engagement Core

REC: Research Education Component

iPSC: Induced pluripotent stem cells

Procedures/Instruments

CDR: Clinical Dementia Rating, a global dementia staging instrument with scores from 0 (cognitively normal) to 0.5, 1, 2, and 3 (very mild, mild, moderate, and severe dementia)

CSF: Cerebrospinal fluid, obtained by lumbar puncture (**LP**)

MRI: Magnetic resonance imaging performed at 3 Tesla (**3T**)

PET: Positron emission tomography

- **PIB**: Pittsburgh Compound B, [^{11}C] amyloid radioligand
- **AV1451**: Flortaucipir; [^{18}F] tau radioligand
- **SUVR**: standardized uptake value ratio

UDS: Uniform Data Set, the standard clinical and cognitive assessment protocol used by ADCs

Note: Unless otherwise stated the reporting period used in this application is from 3/1/14-12/31/18.

This is a new P30 grant application to fund an Alzheimer Disease Research Center (ADRC) at Washington University (WU) in St. Louis. Our ADRC was established in 1985 with the grant, P50 AG05681,that will cease at the end of its 36th budget year on April 30, 2020. This P30 application intentionally builds on and is a natural extension of the existing ADRC. [Note: Charles F. and Joanne Knight generously endowed the ADRC in 2010, and subsequently it has been designated as the Knight ADRC].

A. SIGNIFICANCE

Since inception, the Knight ADRC has been dedicated to providing highly developed services, critical resources, and broad-based expertise to foster and facilitate interdisciplinary, cutting-edge, and impactful basic, translational, and clinical research in Alzheimer disease (AD) at WU and beyond. This research aims to greatly improve the understanding of AD and related dementias (ADRD) so that truly effective therapies may be realized. These efforts fully align with the primary goal of the National Alzheimer's Project Act of 2011, "to prevent and effectively treat ADRD by 2025". The Knight ADRC also is committed to the identification and training of the "next generation" of ADRD investigators, both those who are early-stage as well as those with established careers but who are new to AD research. Considerable efforts are expended by the Knight ADRC to raise awareness of ADRD in the St. Louis community and to engage community members so that they may inform our research efforts and help to assess the effectiveness of our initiatives. In addition to community education, the Knight ADRC provides education about ADRD to our research participants and their families and professional training for students, clinicians, and scientists.

The Knight ADRC is the unquestioned nidus for ADRD research at WU. It features a well-established infrastructure, integrated protocols and approaches, deeply phenotyped research participants, and stable and internationally acclaimed leadership. As a reflection of its productivity, the Knight ADRC has served as the supportive platform for many other affiliated funded projects that address the etiology, pathogenesis, heterogeneity, diagnosis, treatment, and prevention of AD (see Research Strategy, Administration Core). The P30 grant supports affiliated hypothesis-driven studies that utilize ADRC resources. The longstanding major themes of the Knight ADRC are to: 1) distinguish the earliest symptomatic stage of AD from cognitively healthy aging; 2) use molecular biomarkers to characterize the preclinical stages of AD prior to symptomatic onset; and 3) elucidate the complex and multifactorial pathobiology of AD. Many of its affiliated studies explore aspects of those themes. By maintaining "centeredness" across these multiple investigations, the whole of the Knight ADRC represents far more than the sum of its parts. Consequently, the Knight ADRC is recognized locally, regionally, nationally, and internationally for its excellence, productivity, and impact. Several examples illustrate this impact:

A.1. The Clinical Dementia Rating (CDR®) was developed to classify research participants as either cognitively normal (CN; CDR 0) or impaired and, if impaired, to stage the severity of impairment from very mild to severe (CDR 0.5, 1, 2, and 3).(1) Using the CDR to classify participants permits cognitive test performance to serve as a primary outcome measure without the confound that would occur if these test results also were used for classification.(2) In its revised form,(3) the CDR has been widely adopted by the international AD research community as the standard global dementia staging instrument. Its freely available, web-based training and certification paradigms standardize the use of the CDR across clinicians and protocols.(4) A quantitative derivative of the CDR, the CDR SumBox (CDR-SB), often is used as a primary outcome measures in clinical trials of experimental anti-Alzheimer antibodies.(5, 6)

A.2. Early studies by the Knight ADRC proposed the concept of preclinical AD.(7-10) We established that in similarly aged older adults with equivalent Alzheimer neuropathological burden, the preservation of neuronal integrity in the entorhinal cortex distinguishes individuals with preclinical (asymptomatic) AD from those with symptomatic AD.(11, 12) A recent multicenter study of individuals, including Knight ADRC participants, whose brains at postmortem examination had robust AD neuropathology but who were CN during life found that different patterns of cytokine expression may underlie resilient brains with AD.(13) Preclinical AD now is the target of mechanism-based therapies in clinical trials designed to delay or even prevent symptomatic AD.

A.3. Using amyloid PET, the Knight ADRC provided the initial report of preclinical AD in living persons.(14) It also was the first to demonstrate that CN older adults with preclinical AD, as demonstrated by either cerebrospinal fluid (CSF) biomarkers (15) or amyloid PET,(16) are at elevated risk of developing symptomatic AD in comparison with CN biomarker-negative older adults. The Knight ADRC reported: 1) the age-dependent frequency of preclinical AD in CN older adults and the strong correlation of amyloid biomarkers with the *ε4* allele of *apolipoprotein E (APOE)*;(17) 2) the first data-driven characterization of the pathochronology of biomarker changes in preclinical AD, using asymptomatic carriers of mutations in the *amyloid precursor protein (APP)*, *presenilin 1 (PSEN1)*, or *presenilin 2 (PSEN2)* genes;(18) and 3) confirmation of the biomarker-defined stages of preclinical AD(19) as previously hypothesized.(20)

A.4. The Knight ADRC fosters studies of novel mechanisms underlying ADRD pathogenesis.

A.4.1. <u>*APOE* and tau-mediated neurodegeneration</u>: Much evidence indicates that *APOE* influences the risk of AD through its influence on amyloid-beta (Aβ) deposition in both a dose- and isoform-specific manner.(21) Knight ADRC investigators recently demonstrated in P301S tau transgenic mice that *APOE* also affects tau

pathogenesis, neuroinflammation, and tau-mediated neurodegeneration independently of Aβ pathology,(22) suggesting that *APOE* may be a therapeutic target in efforts to reduce tau-mediated neurodegeneration.

A.4.2. Sleep, circadian rhythms, and AD: Data from animal models and humans suggest a bidirectional relationship between sleep and AD.(23) Participants in the Knight ADRC volunteer for home assessment of sleep via three measures collected over six nights: 1) sleep logs; 2) actigraphy; and 3) a single-channel electroencephalograph worn on the forehead (Sleep Profiler™). Non-rapid eye movement (NREM) sleep slow wave activity (SWA) shows an inverse relationship with tauopathy, as measured by CSF assays.(24) Cognitively normal Knight ADRC participants who had positive amyloid PET and/or CSF assays of $A\beta_{42}$ in another study in which actigraphy data were collected over 7-14 days in the home environment showed increased intradaily variability, indicating circadian fragmentation that precedes cognitive dysfunction.(25) In a mouse model of amyloidosis, targeted deletion of the clock gene *Bmal1* results in loss of circadian rhythms and is associated with disrupted Aβ concentrations in the hippocampal interstitial fluid and with increased Aβ plaque accumulation.(26)

A.4.3. Influence of sex and race: A supervised machine-learning algorithm was applied to multiparametric metabolic brain imaging data from CN ADRC participants to derive a "metabolic brain age". Women had a persistently lower metabolic brain age than men, relative to chronological age, although whether this brain "youthfulness" confers resilience to neurodegenerative diseases is unknown.(27) In another study, mean CSF concentrations of total tau (t-tau) and phospho tau (p-tau) were lower in 87 African American participants compared with 816 non-Hispanic white participants and appear to reflect a race by *APOE4* interaction, consistent with possible race-dependent biological mechanisms underlying AD.(28)

A.5. The Knight ADRC supports research into the **heterogeneity** underlying ADRD.

A.5.1. The neuropathological correlates of LOAD versus ADAD: The Knight ADRC serves as the Neuropathology Core for the Alzheimer Disease Neuroimaging Initiative (ADNI; U01 AG024904; M. Weiner, PI). As WU also is the coordinating center for the Dominantly Inherited Alzheimer Network (DIAN; UF1 AG032438; RJ Bateman, PI) that enrolls and follows individuals with autosomal dominant AD (ADAD), the identical neuropathology protocol is used for both "sporadic" late onset AD (LOAD/ADNI, with mean age at death of 82y), and early onset ADAD (DIAN, with mean age at death of 52y). Participants with LOAD who had neuropathological AD frequently had additional pathologies that potentially could contribute to dementia, including synucleinopathy (42%), transactive response DNA-binding protein of 43 kDa (TDP-43), hippocampal sclerosis, infarcts, and argyrophilic grain disease, whereas ADAD cases lacked co-pathologies except for synucleinopathy (50%).(29) These data suggest that ADAD represents a "pure" form of AD whereas LOAD represents AD in conjunction with age and age-associated comorbidities.

A.5.2. ADRD studies: For scientific and budgetary purposes, Core B: Clinical is restricted to enrolling and following longitudinally research participants who are cognitively normal or who have early symptomatic AD to distinguish the earliest symptomatic stages of AD and to characterize the preclinical stages of AD prior to symptomatic onset. However, the Knight ADRC and its investigators are committed to exploring the **heterogeneity** and **multifactorial nature** of AD and to the exploration of non-AD dementias, leveraging its own resources and those of other funded studies to support a large ADRD research portfolio.

A.5.2.1 **Hippocampal sclerosis**: Using clinicopathological resources of the Knight ADRC, visiting scholar Ryoko Ihara, MD, from the University of Tokyo, Japan, used unbiased stereological methods in 1,361 brains from Knight ADRC individuals to identify 93 cases (6.8%) of hippocampal sclerosis (HS); the prevalence of HS increased to 11.5% in individuals who died at age 90y or greater.(30) TDP-43 was present in 92% of HS cases. The cognitive impairment of HS phenotypically resembles AD dementia.

A.5.2.2. **Longitudinal Early-Onset Alzheimer Disease Study (LEADS):** The **heterogeneity** of AD also is being explored in the Knight ADRC through its participation as a performance site (G.S. Day, site PI) in this multicenter study (U01 AG057195; L Apostolova, PI) of individuals with mild symptomatic AD with onset between 40-64 years of age who lack a known pathogenic mutation for AD. Computerized cognitive batteries, blood for DNA, brain MRI, amyloid PET, and CSF biomarkers in these individuals will be compared with data from persons with "sporadic" late-onset AD to study differences in disease progression. To date, the Knight ADRC has enrolled 8 participants in LEADS.

A.5.2.3. **Human immunodeficiency virus** (HIV): Knight ADRC faculty Beau M. Ances, MD, PhD, and colleagues compared cerebral tau burden as determined by flortaucipir PET in individuals with symptomatic AD who are followed in the Knight ADRC with HIV-positive and HIV-negative persons, age 50y and older, and found that tau PET SUVR was similar in HIV-positive and HIV-negative persons whereas symptomatic AD

persons had elevated SUVRs. These findings suggest that older HIV-positive individuals are not at risk for tau-mediated neurodegeneration.(31)

A.5.2.4. **Frontotemporal lobar degeneration** (FTLD). As a performance site for the Longitudinal Evaluation of Familial Frontemporal Dementia Subjects (LEFFTDS; U01 AG045390) and the Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL; U54 115092089) studies, 25 participants have been enrolled and followed in the combined studies at WU (Nupur Ghoshal, MD, PhD, site PI); 22 participants remain active. The Genetics and High Throughput -Omics Core of the Knight ADRC longitudinally follows members of several FTLD families, including the largest known pedigree with a *GRN* mutation as well as a family with a *MAPT* R406W mutation. Dermal fibroblasts harvested from individuals from these families are induced into pluripotent stem cells (iPSCs) from which neurons are derived and now maintained in the Knight ADRC's Biomarker Core to allow gene expression studies.(32).

A.5.2.5. **Neurodegeneration in Aging Down Syndrome** (NiAD). The Knight ADRC, in conjunction with WU's Intellectual and Developmental Disabilities Research Center, has joined the NiAD consortium (U01 AG051406; Benjamin Henden, Bradley Christian, William Klunk, PIs) as a performance site with Beau Ances as site leader. Recruitment will be initiated for adults with Down syndrome (DS) at WU for assessment with the NiAD protocol, including imaging and CSF biomarker studies. A Knight ADRC pilot grant award (33.3) to Christina Lessov-Schlaggar in 2016 established the feasibility of enrolling DS individuals for NiAD assessments (33 DS participants were enrolled and assessed in 12 months).

A.5.2.6. **Biomarkers Across Neurodegenerative Diseases** (BAND). Brian Gordon, PhD, of the HASD Imaging Core has been awarded a grant, co-funded by the Alzheimer Association, the Michael J. Fox Foundation, the Weston Brain Institute, and Alzheimer Research UK, to study CSF and plasma biomarker profiles in individuals with symptomatic AD and **Parkinson disease** (PD). The Knight ADRC cohort, including CN, preclinical AD, and symptomatic AD persons, will be leveraged with the WUSM Movement Disorders Center cohort of CN and impaired PD individuals to compare CSF levels of Aβ, tau, α-synuclein, and neurofilament light (NfL) to learn if these pathologies act synergistically to worsen clinical trajectories.

A.5.2.7. **Neuroinflammation**. The HASD Imaging Core Leader, Tammie Benzinger, MD, PhD, previously established the validity of the neuroinflammation biomarker, diffusion basis spectrum imaging (DBSI), in multiple sclerosis. She and her colleagues now extend this research to AD with both *in vivo* PET in Knight ADRC participants and *ex vivo* validation in postmortem brains (R01 AG054567; T Benzinger, Y Wang, co-PIs). A preliminary immunohistochemical study of neuroinflammation in postmortem brain tissue from 4 CN, 6 AD, and 5 PD individuals indicated that astrocytosis contributes to cerebral white matter demyelination in AD, PD, and aging.(33)

A.5.2.8. **Exploring the multifactorial nature of AD by examining the role of the neurovascular unit in AD**: The Knight ADRC collaborates with the University of Southern California ADRC and the ADCs at the Mayo Clinic (Rochester, MN) and the Banner Alzheimer's Institute (Phoenix, AZ) in a Program Project Grant, "Vascular contributions to dementia and genetic risk factors for Alzheimer disease", (P01 AG052350; B. Zlokovic, A. Toga, co-PIs). Novel imaging techniques, including dynamic contrast-enhanced MRI (DCE), examine the **brain's vascular integrity** in participants with and without an *APOE4* allele. As part of this collaboration, over 100 Knight ADRC participants thus far have had DCE studies to permit quantification of the permeability of the blood-brain barrier.(34)

A.5.2.9. **Statistical modeling of Aging and Risk of Transition** (SMART): This consortium grant (R01 AG386561; R Kryscio, E, Abner, co-PIs) uses data from several high quality longitudinal studies of aging and cognition (Knight ADRC; Oregon Brain Aging Study; Sanders-Brown Healthy Brain Aging; the Nun Study; the Honolulu Asia Aging Study; the Religious Orders Study; the African American Dementia and Aging Project; the Klamath Exceptional Aging Project) to examine longitudinal cognitive trajectories and other factors associated with **mixed neuropathologies**, such as AD with co-occurring with cerebrovascular disease. Together, these studies have followed ~11,540 participants and obtained ~3,000 autopsies.

A.5.2.10. **Other Non-AD disorders**. Clinical Core investigator Gregory S. Day, MD, MSc, utilized the patient resources of the Memory Diagnostic Center (MDC), the outpatient faculty practice of the Knight ADRC investigators (including Morris, Holtzman, Bateman, Snider, and Day), for a clinicopathological comparison of **corticobasal degeneration** (CBD) and symptomatic AD. The initial presentation of CBD may mimic symptomatic AD, and AD neuropathologic change is present postmortem in 59% of CBD cases.(35) Dr. Day and colleagues also evaluated flortaucipir-tau PET retention in 5 individuals with subsequent autopsy-confirmed sporadic **Creutzfeldt-Jakob disease** (CJD) in comparison with tau retention in CN Knight ADRC

participants and those with symptomatic AD. There were no differences in uptake patterns between CJD patients and CN persons but SUVRs were elevated in symptomatic AD.(36)

A.6. The Knight ADRC supports drug development, secondary prevention studies, and clinical trials of anti-Alzheimer therapies.

A.6.1. Knight ADRC Associate Director David M. Holtzman, MD, develops antibodies as potential therapies for AD. The murine monoclonal antibody to Aβ, m266, was found by the Holtzman laboratory to bind soluble Aβ, decrease the accumulation of Aβ plaques, and improve behavior in *APP* transgenic mice.(37) This antibody and its sequence were licensed to Eli Lilly and Company, where it was humanized as solanezumab. It no longer is in trials of individuals with symptomatic AD, but continues as the therapeutic agent in two secondary prevention trials, the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) trial(38) and the DIAN-Trials Unit (DIAN-TU).

The Holtzman laboratory developed an antibody, HJ8.5, to tau protein(39) that was licensed to C2N Diagnostics, LLC, which was co-founded by Holtzman and Randall J. Bateman, MD, who also is an Associate Director of the Knight ADRC. After the antibody was humanized, C2N licensed it to AbbVie, which is sponsoring two human trials of the antibody: one in individuals with symptomatic AD, the other in individuals with progressive supranuclear palsy. The Holtzman laboratory also has developed an antibody, HAE-4, that is directed toward non-lipidated ApoE and removes cerebral amyloid deposits in mouse models;(40) it was licensed to Denali Therapeutics but has not yet advanced to clinical trials.

A.6.2 Knight ADRC investigator Tim Miller, MD, PhD, has developed a tau-lowering antisense oligonucleotide (ASO) in conjunction with Ionia Pharmaceuticals. This drug has entered clinical trials in early symptomatic AD in Europe. The Miller Laboratory also has developed an ASO that appears to convert the 4R tau isoform to the 3R isoform and is exploring its therapeutic potential.

A.6.3. The inaugural secondary prevention trial with anti-amyloid therapies. The first-ever secondary prevention trial of mechanism-based experimental therapies for AD was launched at WU in December, 2012, by the DIAN-TU, largely in asymptomatic mutation carriers from ADAD families.(41) This international, adaptive design, secondary prevention trial has two therapeutic arms, one with solanezumab (anti-soluble Aβ) and the other with gantenerumab (anti-fibrillar Aβ). Full enrollment (N = 194 randomized participants) was achieved in 2015; follow-up will determine whether these antibodies can prevent cognitive decline in CN persons.

A.6.4. Performance site for sponsored clinical trials in the current budget period. In addition to the A4 study (15 participants randomized), the Knight ADRC served as a performance site for Lilly's NAVIGATE-AD trial of LY3202626, developed as an inhibitor of β-site amyloid precursor protein-cleaving enzyme (BACE), in individuals with mild symptomatic AD. Ten participants were randomized before the trial was terminated in 2018. Ten mildly symptomatic AD participants also were randomized in Biogen's ENGAGE Phase 3 trial of aducanumab until it was terminated in 2019. Four mildly symptomatic AD participants have been randomized to date in Lilly's TRAILBLAZER Phase 2 trial of LY3002813, an antibody to plaque-based $A\beta_{42}$.

A.7. The Knight ADRC is accelerating the development of novel AD diagnostics.

A.7.1. The Stable Isotope Labeling Kinetics (SILK) method, developed by Dr. Bateman and colleagues, measures the central nervous system (CNS) production and clearance of targeted proteins, such as Aβ.(42) In addition to clarifying how Aβ metabolism is dysregulated in AD, the technique enables the effects of drugs targeting Aβ (or other proteins) to be measured.(43)

A.7.2. Adaptation of the SILK technique for human plasma studies. Forty-one Knight ADRC participants (18 with positive amyloid PET scans) underwent 20 serial blood draws over a 24-hour period after an intravenous bolus of $^{13}C_6$ leucine. After immunoprecipitation, plasma samples were subjected to liquid chromatography tandem mass spectrometry (LC/MS). Amyloid-positive participants had a faster fractional turnover of $A\beta_{42}$ relative to $A\beta_{40}$ and had lower plasma $A\beta_{42}$ concentrations.(44) A follow-up study with 158 Knight ADRC participants with high precision immunoprecipitation and LC/MS measures of plasma and CSF confirms that plasma $A\beta_{42}/A\beta_{40}$, when combined with age and *APOE4* status, accurately diagnoses brain amyloidosis (as determined by amyloid PET). These findings suggest that the plasma ratio of $A\beta_{42}/A\beta_{40}$ is a viable screening method for the presence of brain amyloidosis in older adults.(45)

A.7.3. Remote cognitive monitoring: Two of the Knight ADRC's affiliated grants, the DIAN observational study and the HASD PPG (starting May 1, 2019, renewed for budget years 36-40) have incorporated a protocol to obtain reliable and repeatable cognitive assessments in naturalistic settings (e.g., home), using a smartphone application for iOS and Android, in which the brief tests are administered in a measurement burst design.(46) Knight ADRC participants are included in the HASD study (Project 4, J Hassenstab, Project Leader).

A.8. Philanthropy is essential to the Knight's ADRC initiatives, as our NIA grants support ~70% of our budgetary requirements whereas the remaining ~30% is sustained by gift funds. In the current budget period, substantial new gifts to support the Knight ADRC program have been secured with important assistance from Dean David Perlmutter (see Letter of Support) and the School of Medicine's Alumni and Development Office. These gifts include:

A.8.1. A gift of $2.6 million in expendable funds from Joanne Knight and her family. This new gift is in addition to the endowment in 2010 that resulted in the naming of the Knight ADRC in honor of Mrs. Knight and her now deceased husband; the Knight ADRC benefits annually from the income from the endowment.

A.8.2. An estate gift of $5.5 million from a grateful patient of Dr. Morris. A portion of this gift was used for an endowed professorship for the Knight ADRC that in 2018 enabled Beau Ances, MD, PhD, to become the inaugural Daniel J. Brennan, MD, Professor of Neurology. The majority of the remaining funds are in an endowment to support the Knight ADRC.

A.8.3. A gift of $10 million in expendable funds was made in March, 2019, to the Knight ADRC, by another of Dr. Morris' grateful patients.(47)

A.8.4. The Centene Corporation has completed a $100 million gift to WU. From this gift, $2 million/year for 10 years will support precision medicine and basic and translational research into ADRD biomarkers, the biology of innate and adaptive immunity, APOE, tau, sleep, and circadian rhythms; several Knight ADRC investigators in this application will benefit from this gift, including Drs. Holtzman, Bateman, Karch, and Cruchaga.

A.9.The Knight ADRC and its faculty are privileged to contribute to the national network of ADCs and to the broader Alzheimer community.

A.9.1. The Knight ADRC Director, Morris, chairs the External Advisory Committee (EACs) for the ADCs at Boston University, University of Pennsylvania, Johns Hopkins University, Mayo Clinic, University of Wisconsin, University of Southern California, and University of California-Irvine. He also serves on the EAC for the LEFFTDS and ARTFL studies.

A.9.2. In 2017, Morris chaired a NIA-commissioned group of investigators from 10 ADCs who developed non-mandatory Guidelines for EAC visits that were provided to all 31 ADCs.

A.9.3. Knight ADRC Associate Director Holtzman serves on the National Advisory Council for Aging for the NIA. Dr. Holtzman also is the current President of the American Neurological Association.

A.9.4. Dr. Gregg Day is a member of the American Academy of Neurology's "Guideline Development, Dissemination, and Implementation" Subcommittee and is leading the systematic review of the literature to update guidelines for dementia diagnoses.

A.9.5. The Knight ADRC contributes its participant data to the National Alzheimer's Coordinating Center (NACC) and blood, DNA, and brain tissue to the National Centralized Repository for Alzheimer Disease and Related Dementias (NCRAD). The 1517 phase 2 samples provided to NCRAD are the second most among all ADCs (see Letter of Support from Dr. Tatiana Foroud).

A.9.6. Executive Director Moulder served on the ADC Administrators' Steering Committee from 2013-2016 (Chair, 2015-2016).

A.9.7. The first participant enrolled in ADNI was from the Knight ADRC in 2005. Currently 15 participants are active in ADNI3 at WU; Dr. Ances is the ADNI site PI. The ADNI Neuropathology Core is at the Knight ADRC (JC Morris, Core Leader).

A.9.8. The Knight ADRC supports performance sites at WU for the following national multicenter studies: 1) Neurodegeneration in Aging Down Syndrome (NiAD), B. Ances, site PI; 2) Longitudinal Early-Onset Alzheimer Disease Study (LEADS), G. Day, Site PI; and 3) ARTFL and LEFFTDS, to be united as the ARTFL-LEFFTDS Longitudinal FTD Study (ALLFTD), N. Ghoshal, site PI.

A.9.9. B Joy Snider, MD, PhD, serves on the Steering Committee for the Alzheimer Clinical Trials Consortium.

A.10. The Knight ADRC has a long tradition of transdisciplinary research. Knight ADRC investigators represent the following 14 Departments and Divisions at WUSM: Neurology, Psychiatry, Biochemistry, Geriatrics, Genetics, Pathology (Neuropathology), Radiology, Biostatistics, Otolaryngology, Ophthalmology, Emergency Medicine, Obstetrics and Gynecology, Physical Therapy, and Occupational Therapy. Outside the School of Medicine, Knight ADRC investigators also hail from WU's College of Arts and Sciences (Departments of Psychological and Brain Sciences, Political Science, Biology, and Chemistry) and the School of Social Work.

A.11. The Knight ADRC supports affiliated research. Knight ADRC investigators, participants, and their data are highly valued by investigators and programs, both internal and external to WU, as evidenced by many

requests (see below). The Knight ADRC has a well-established infrastructure that facilitates our rapid and broad sharing of data and biospecimens. In this reporting period:

A.11.1. Thirty-eight requests for access to participants were fulfilled.

A.11.2. Eighty-two requests for access to biospecimens were fulfilled.

A.11.3. These fulfilled requests were to investigators awarded grants totaling nearly $300 million; "second generation" grants leveraged from this support totaled $44 million (see Core A: Administration).

A.11.4. Publications: In the current budget period, 341 publications were directly supported by Knight ADRC resources; another 243 publications were indirectly supported by the Knight ADRC (e.g., contributions to consortium data; faculty serving as authors on non-Knight ADRC studies); per the RFA, the list of publications is not included with this application.

A.11.5. Collaborative grants. In 2018-2019 alone, the following R01s were funded by NIA and each will feature the Knight ADRC in major roles:

A.11.5.1. **RF1 AG059009; M Weiner, PI**: "Validation of online measures to predict and monitor cognitive decline". This grant will develop, implement, and optimize online instruments to measure cognitive and functional information on participants in the Brain Health Registry; the CDR will be modified as an eCDR. Optimization and validation studies will use cohorts at the University of California, San Francisco, the University of Alabama-Birmingham, the Mayo Clinic, and the Knight ADRC.

A.11.5.2. **R01 AG058676; C Masters, PI:** "Alzheimer's dementia onset and progression in international cohorts". Existing longitudinal data from 5 established cohorts (Adult Children Study; ADNI: Australia Imaging, Biomarkers, and Lifestyle study (AIBL); NACC; and DIAN) will be examined for factors that influence age at symptomatic onset and rate of AD progression and for comorbidities such as vascular disease.

A.11.5.3. **RF1 AG059869; M Albert, PI**: "Preclinical AD Consortium". This study focuses on CN cohorts of middle age individuals who are at risk of AD due to a parental history. The cohorts include the Adult Children Study, the Baltimore Longitudinal Study of Aging, AIBL, BIOCARD, and the Wisconsin Registry for Alzheimer Prevention. The study will examine potential factors, such as cognitive reserve, that confer protection or resilience to developing symptomatic AD. White matter hyperintensities and other factors associated with an earlier age symptomatic onset will be studied.

A.12. Progress of Knight ADRC projects in the current funding period.

A.12.1. Project 1: Correlation of tau PET imaging with CSF AD biomarkers, AM Fagan, Project Leader: 201 Knight ADRC participants have completed tau PET as part of this project (target was 80). Significant relationships were present for all CSF biomarkers and tau tracer uptake, particularly for CSF t-tau and p-tau, in the medial temporal, parietal, and frontal cortices.(48) The spatial distribution of tau is more widespread than predicted by pathological staging and correlates with measures of early cognitive dysfunction.(49) Tau-related cognitive decline is worse in individuals with high amyloid burden; multiple biomarkers stage AD progression.(50)

A.12.2. Project 2: Synergy of Aβ clearance mechanisms in vivo, JR Cirrito, Project Leader: Using microimmunoelectrode (MIE) technology to study the kinetics of Aβ clearance in the brains of living mice, multiple clearance rates of Aβ were found to be regulated by various clearance pathways.(51) AMPA stimulation decreases Aβ levels in the interstitial fluid by 50% via an interleukin-6-dependent clearance mechanism.(52) Dr. Cirrito has been awarded a 2019 grant of $250,000 over 2 years from the Coins for Alzheimer's Research Trust (CART) to continue his investigations of Aβ clearance pathways.

A.12.3. Project 3: Circadian rhythms in regulation of Aβ pathology and brain oxidative stress, ES Musiek, Project Leader: Actigraphy and AD biomarker data in 189 cognitively normal Knight ADRC participants demonstrated fragmentation of circadian rhythms in the preclinical stage of AD.(25) Genetic disruption of the circadian clock accelerates Aβ plaque deposition in the brains of mouse models of AD, supporting an effect of circadian dysfunction on Aβ pathology.(26)

B. INNOVATION

Section A. Significance provides examples of how the Knight ADRC has made major and often pioneering contributions to new approaches in the understanding of ADRD etiology: *APOE4* and tau; an *APOE4* by race interaction; bidirectional relationship of AD and sleep/circadian rhythms; diagnosis (e.g., the multimodal molecular biomarker characterization of preclinical AD); the SILK technique for plasma Aβ; treatment advances (e.g., development of new antibodies to Aβ and tau), exploration of the heterogeneity and multifactorial nature of AD (e.g., the Zlokovic/Toga PPG to examine vascular contributions to dementia); and prevention (the first-

ever secondary prevention trial with mechanism-based therapies for AD was launched in 2012 by the DIAN-TU). This application features other novel concepts, approaches, and methodologies.

B.1. Racial differences in CSF biomarkers of AD have been reported by investigators at Emory University(53) and by us.(28) A major limitation of such studies is the relative paucity of biospecimens from under-represented groups. To address this issue, the Knight ADRC hosted a national Workshop in October, 2018, to propose new strategies to increase "African American Participation in Alzheimer Research" (R13 AG059415; JC Morris, PI). As those strategies are being developed and tested, the Knight ADRC has inaugurated **a collaboration with the Emory ADRC to share aliquots of CSF and plasma from African American participants** (see Core A: Administration; 158 aliquots of CSF and 169 aliquots of plasma from Knight ADRC participants already have been shipped to the Emory ADRC). This collaboration, which is supported by an award of $600,000 from the Cure Alzheimer Fund, will include biofluids already collected as well as those to be collected prospectively and will enable both ADRCs to substantially increase the sample sizes for African American biomarker studies beyond what either ADRC could accomplish alone (another public-private partnership; see Overall Letter of Support from Dr. Allen Levey).

B.2. The Knight ADRC's goal of characterizing preclinical AD requires its research participants to complete the imaging and fluid biomarker protocols at a high rate. Hence, interested individuals are enrolled in the Knight ADRC's clinical cohort only if they are eligible for and in principle willing to complete these studies (i.e., MRI, PET, CSF and blood collection). (It is appreciated that the trade-off for this emphasis on biomarker completion is that our cohort is unlikely to be representative of the general population. Also, the expectation for LP in African Americans is waived as we experienced a sharp decrease in African American participation when it first was proposed). In this application, we implement a new **recruitment strategy that enriches the clinical cohort with individuals with preclinical AD** by preferentially enrolling individuals who at baseline have a positive amyloid PET scan (see Core B: Clinical and Overall Human Subjects for a detailed description of this strategy).

B.3. The NIA's budgetary limit for this new P30 application is insufficient to fund the scope of work that is proposed under the umbrella of the Knight ADRC. Hence, we innovatively encourage that other funded studies be leveraged in support of Knight ADRC goals while maintaining strict fiscal integrity so that there is no violation of individual grant budgetary restrictions. For example, much of the proposed work of the Genetics and High Throughput -Omics Core will capitalize on R01s awarded to the Co-Leaders of the Core, Drs. Cruchaga and Harari, who will make data generated from biospecimens from Knight ADRC participants in their R01s available for Knight ADRC analyses (supported by the Knight ADRC budget). Similarly, for more than a decade the Knight ADRC participants have their blood and CSF collection by the ACS Biomarker Core (P01 AG026276; JC Morris, PI; see Letter of Support from Anne Fagan, PhD, in Clinical Core); similar leveraging of imaging data in Knight ADRC participants uses the Imaging Core of the Healthy Aging and Senile Dementia study (P01 AG03991; JC Morris, PI; see Letter of Support from Tammie Benzinger, MD, PhD, in Clinical Core). Because of these successful arrangements, the new Biomarker Core in this Knight ADRC application focuses on bringing a new modality, iPSCs, to our biomarker portfolio.

C. APPROACH

C.1. Features of the Knight ADRC. The Knight ADRC fulfills all criteria for a successful ADRC program. Using clinical, cognitive, imaging, fluid biomarker, and genetic/genomic measures, it is focused on the characterization of the preclinical (asymptomatic) stage of AD. As detailed in A. Significance, the Knight ADRC has contributed uniquely and substantially to the ADRD field. Its highly experienced Director is internationally recognized for his scientific and administrative abilities; both Associate Directors share these same attributes. Washington University provides sufficient space, positions, and other resources to enable the Knight ADRC to fulfill its scientific mission. For over 3 decades, the Knight ADRC has utilized the organizational capabilities of WU to capitalize on its rich and extensive neuroscience community to further its broad portfolio of basic, translational and clinical scientific initiatives. The WUSM has supported the Knight ADRC with dedicated physical space sufficient for its research. A hallmark of the Knight ADRC has been its transdisciplinary collaborative approach that increases the productivity and value of its research. This collaborative approach is realized both at WU and through its extensive interactions with programs and investigators, both nationally and internationally. The quality of the Knight ADRC is underscored by the numerous requests by investigators, both internal and external to WU, for access to its participants and their data and biospecimens, which are freely shared by the Knight ADRC.

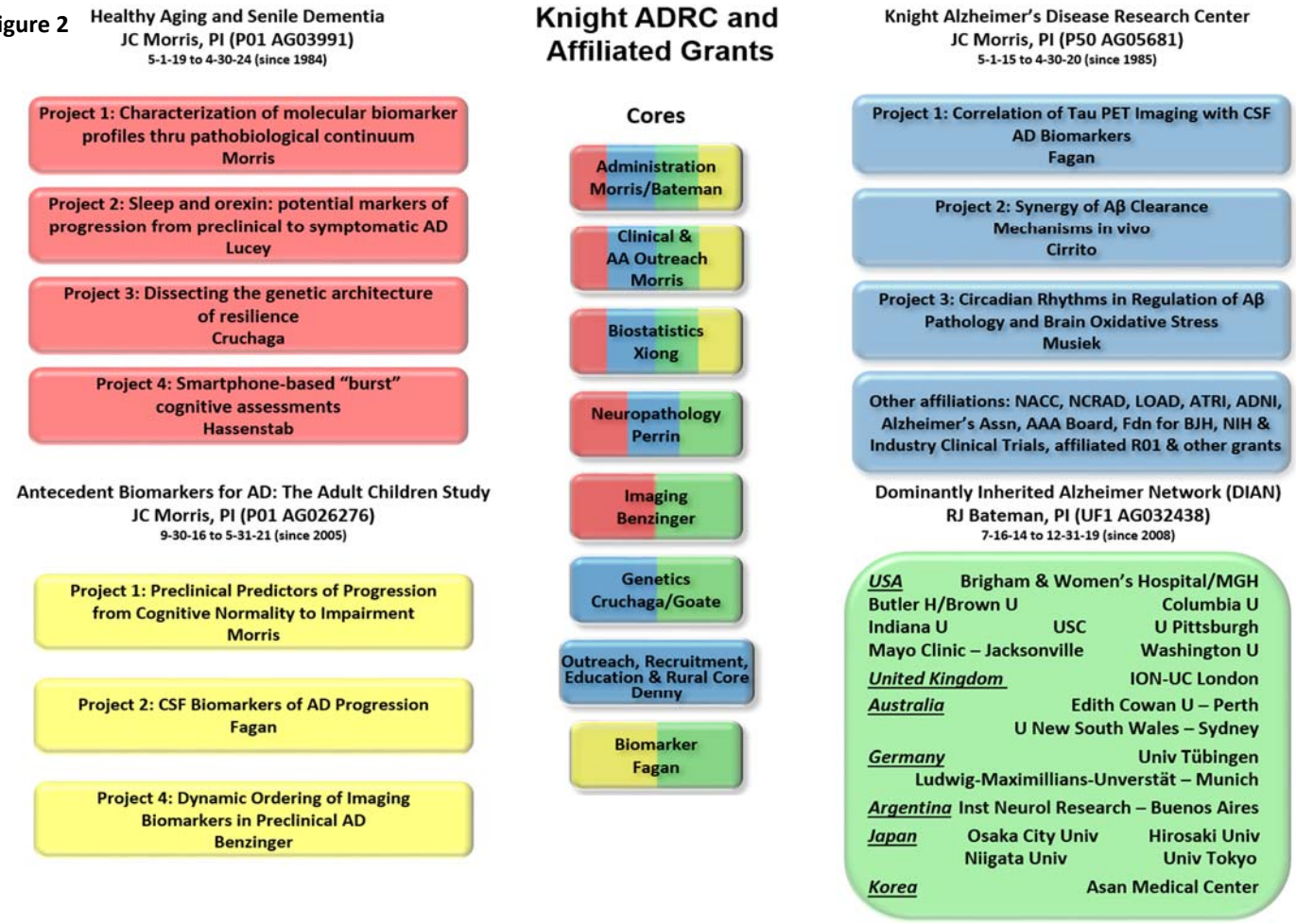
C.2. Organization and Administration.

C.2.1. The Knight ADRC benefits from stable leadership. Dr. Morris has led Core B: Clinical since 1991, shared co-leadership of the ADRC with Eugene Johnson, PhD, from 1997 to 2003, and has been Director and PI since 2003. Dr. Morris benefits from his Associate Directors, David M. Holtzman, MD, and Randall J. Bateman, MD; both are internationally recognized for their impactful scientific contributions to AD. Dr. Morris' previous ADRC Executive Director, Virginia Buckles, PhD, plans to retire at the end of June, 2019. Thus, in 2017 former Associate Executive Director Dr. Krista Moulder became Executive Director for the Knight ADRC, HASD, and ACS while until retirement Dr. Buckles now serves as Associate Executive Director. Morris has charged all Core Leaders in the Knight ADRC to identify a faculty member whom they can mentor over a suitable time period to be prepared, should the occasion arise, to assume leadership of the Core; the transition from Buckles to Moulder is an illustration of this paradigm. Drs. Moulder and Buckles have their offices contiguous with Dr. Morris' office in the administrative suite of the Knight ADRC building on the WUSM campus; Dr. Bateman's office is one floor above Dr. Morris' office in the same building. Each Wednesday from 7:00am-8:00am, Drs. Holtzman, Bateman, Moulder, and Buckles join Dr. Morris in his conference room for the Knight ADRC Executive Committee Meeting (see Core A: Administration).

From the prior Knight ADRC renewal application (prepared in 2014), the Leaders of the Administration (Morris), Clinical (Morris), Data Management and Statistics (Xiong), and ORE (Denny) Cores remain in their positions in this application. Smooth leadership transitions occurred for two Cores in the current budget period. Former Genetics Core Leader Alison Goate, DPhil, relocated in 2015 to the Icahn School of Medicine at Mount Sinai and, in accordance with the model described above, was succeeded as Core Leader by her former mentee, Carlos Cruchaga, PhD; with this application, Oscar Harari, PhD, joins Cruchaga as Co-Leaders of the Core. Neuropathology Core (NPC) Leader Nigel Cairns announced in 2017 that he would retire, effective August 31, 2018, and mentored the Associate NPC Leader, Richard Perrin, MD, PhD, such that Dr. Perrin readily assumed all responsibilities as Knight ADRC NPC Leader on September 1, 2018.

The organizational structure of the Knight ADRC and its affiliated multicomponent grants is shown in Figure 2. The leadership of the combined Cores (including the REC and ADRC Biomarker Core, not shown as they are not yet funded) includes five men (Morris, Xiong, Perrin, Cruchaga, and Harari) and six women (Benzinger, Fagan, Denny, Karch, Snider, and Stark). Two Core Leaders (Cruchaga and Harari) identify as Hispanic.

Figure 2



These multicomponent grants are linked thematically by their focus on characterizing preclinical AD. The PPGs Healthy Aging and Senile Dementia and The Adult Children Study are imaging and CSF biomarker studies of preclinical AD at different ages: HASD focuses on the transition from CN aging to symptomatic AD in individuals 65y and older, whereas ACS explores the initial onset of biomarker abnormalities and their rate of change in CN individuals, age 45y – 74y, who have an affected parent with AD. The DIAN study enrolls a special group of adult children whose affected parent had a single gene mutation causing AD. These affiliated grants are complementary and synergistic with the Knight ADRC. Recruitment for the Knight ADRC, HASD, and ACS clinical cohorts primarily is by "word of mouth" for persons living in the greater St. Louis metropolitan statistical area and is accomplished with identical screening and intake tools and administered by the same personnel. All four grants utilize the same clinical assessment office, the Memory and Aging Project (in the Knight ADRC building) and the same clinicians, nurses, psychometrists, social workers, and other personnel. The clinical and cognitive assessment batteries for the Knight ADRC and the HASD cohorts are identical and incorporate the UDS, Version 3, of the NACC; the ACS and DIAN also incorporate the UDS but the cognitive batteries are modified to reflect the younger ages of these cohorts. All Knight ADRC, HASD, and ACS participants 65y and older are assessed annually (ACS participants age 45y-64y are assessed every 3 years). All participants are eligible for and (in principle) willing to complete all biomarker studies, which are obtained at baseline and every 3 years thereafter. Each participant enrolled into a specific grant remains supported by that grant for all baseline and longitudinal assessments and procedures (that is, each grant is budgetarily distinct from the others and is responsible for the costs associated with its own cohort). Because participants 65y and older are assessed identically across the Knight ADRC, HASD, and ACS, they can be combined into a Total Registry (TR) for analytic purposes. The TR of 65y and older participants currently has 686 individuals, greater than any individual grant can support alone.

C.2.2. The Knight ADRC actively fosters new research projects. Federal grants to investigators, both at and external to WU, who used and benefitted from Knight ADRC resources in this budget period total $295,718,833 in research funds; another $22,471,400 in non-federal research funds used Knight ADRC resources. In this budget period, recipients of Knight ADRC resources subsequently were awarded another $43,732,274 in "2nd generation" grants. The Knight ADRC now transitions from the P50 model of supporting 3 R01-type research projects of 5 years duration, plus three 1-year pilot projects annually, to inaugurating Developmental Projects. These Projects will support early-stage investigators or established investigators who are new to ADRD with $100,000 a year for up to 2 years. Two Developmental Projects are anticipated to be in progress at any point in time (See Core A: Administration).

C.2.3. The Knight ADRC provides an exceptional training environment for students, residents, visiting scholars, fellows, and early-stage investigators (ESIs). With this application, we propose a Research Education Component (REC) to coordinate our professional training opportunities and to optimize the career development programs for what will be the "next generation" of ADRD investigators (see REC). The REC will leverage a new T32 fellowship program awarded to B. Joy Snider, MD, PhD, in 2018 (T32 AG058518; BJ Snider, PI). In its first year, the T32 is supporting two postdoctoral fellows: Dr. Melissa Budelier and Dr. Rachel Hendrix. Since 1998, Dr. Morris has funded the Knight ADRC Postdoctoral Fellowship in dementia using discretionary funds and the income from an endowed philanthropic fund. This two-year un-accredited fellowship is tailored to the individual's research interests, which range from clinical research to bench science, with the goal of introducing the fellow to the translational and clinical research experiences of the Knight ADRC. Fellows initiate, conduct, complete, and publish at least one research project, and are positioned in the 2nd year of the fellowship to submit an application for a K or similar award. All fellows are mentored clinically in aspects of aging and dementia by Dr. Morris; some also pursue a basic or translational science project in the laboratory of another Knight ADRC faculty member. In the next budget period, the Knight ADRC Postdoctoral Fellowship will be part of the REC's training portfolio. (See the REC for a list of past Knight ADRC fellows).

The Knight ADRC also brings investigators who are established in other biomedical areas to ADRD research. In the current budget period, Gregory Van Stavern, Associate Professor of Ophthalmology and Visual Sciences, an expert in the ocular manifestations of idiopathic intracranial hypertension,(54) began to explore the utility of optical coherence tomography angiopathy in detecting retinal changes associated with AD in Knight ADRC participants. He and colleagues found that persons with preclinical AD have retinal microvascular abnormalities affecting the foveal avascular zone that potentially could serve as a preclinical screening tool.(55) Dr. Van Stavern and colleagues are seeking funding to examine these findings longitudinally. Jinbin Xu, Assistant Professor of Radiology, used quantitative autoradiography to examine striatal dopamine pre-synaptic markers and receptors in rat models, but has now extended his research to

examine neuroinflammation and myelin status in the white matter of postmortem brains obtained from the Knight ADRC(33) in Alzheimer disease, Parkinson disease, and normal aging brains.

In the final budget year (5/1/19-4/30/20) of the current funding cycle, the Knight ADRC supports four pilot grants as follows: 1) Brian Edelson, MD, PhD, Assistant Professor of Pathology and Immunology, for the "Characterization of CSF microglia in Alzheimer disease"; 2) Meredith Jackrel, PhD, Assistant Professor of Chemistry, for the "Potential Hsp104 variants to disaggregate Aβ and tau pre-amyloid oligomers and fibers": 3) Keith Hengen, PhD, Assistant Professor of Biology, for the "Continuous evaluation of network dynamics in P301S/E4 mice"; and 4) Andrew Aschenbrenner, PhD, Instructor in Neurology, for "Validating an online test to assess cognitive effort in Alzheimer disease". Drs. Edelson, Jackrel, and Hengen all are new to ADRD research; Jackrel and Hengen are in WU's College of Arts and Sciences, indicative of the broad presence the Knight ADRC demonstrates in the entire WU community (see Letters of Support from Chancellor Wrighton and Chancellor-Elect Martin).

C.3. Institutional support. The Department of Neurology at WUSM is the administrative "home" for the Knight ADRC; the Department Chair; David Holtzman, MD, is an Associate Director of the Knight ADRC. The Knight ADRC enjoys exceptional institutional support from WU/WUSM. David H. Perlmutter, MD, Executive Vice Chancellor for Medical Affairs and Dean of WUSM, provides the Knight ADRC with $100,000 annually in support of our research programs (see Letter of Support). He also provided 1,800 square feet of new space (with renovations) for the Imaging Core of HASD and 2,225 square feet for the Biomarker Core of ACS. Additionally, the Dean provided new space of 2,700 square feet for the DIAN-TU. Dean Perlmutter very effectively has supported the Knight ADRC in securing new philanthropic support.

C.4. AD/ADRD Research Implementation NAPA Milestones; Core contributions

C.4.1. The Administration Core, and indeed the entire Knight ADRC, supports the accelerated development of biofluid molecular signatures that target a variety of disease processes (neuroinflammation; CSF SNAP-25 and Neurogranin to interrogate synaptic integrity), including in asymptomatic persons, and link peripheral molecular signatures with imaging and CSF biomarkers (M9.B). It also supports, in collaboration with the DMS Core, increased transparency in the reporting and reproducibility of research finding (M3.C), makes the datasets widely available (M3.A), and in collaboration with the NPC, rapidly distributes clinical data and biosamples collected from our racially diverse clinical cohort (M.4.D). It has obtained supplementary funding (R13; Cure Alzheimer Fund) to support research in diverse communities (M12.A) and enables access to Knight ADRC data to assess the predictive value of biomarkers and advance understanding of disease heterogeneity (Zlokovic/Toga PPG; Masters R01; Albert RF1; Krysicio R01; Gordon BAND study) (M3.D).

C.4.2. The Clinical Core supports the development of remote cognitive monitoring of participants in naturalistic settings through a smartphone application that provides measurement burst cognitive testing (this application is released as open access) (M9.H; M11.C), and compares cognitive function and impairment in African American and white participants (M19.C.4).

The Core supports longitudinal molecular endophenotyping of existing cohorts that include African Americans as well as new at-risk cohorts, including Down syndrome (NiAD), autosomal dominant AD (DIAN), and early-onset non-mutation AD (LEADS) (M1.A).

The Core supports research regarding sex differences in trajectories of brain aging(27) (M2.0), research that addresses circadian rhythms and sleep(25) (M2.F), and has incorporated a life course approach to explore AD risk in minorities (see Clinical Core Letter of Support from Dr. Lisa Barnes) (M2.J).

The Core advances understanding of vascular contributions to dementia (M22.A.1) and explores multiple disease mechanisms across neurodegenerative disorders through its collaboration with the Neuropathology Core and by its participation in funded studies (Zlokovic/Toga PPG; Albert RF1; Masters R01; Kryscio R01; Gordon BAND study).

C.4.3. The Data Management and Statistics Core, in collaboration with the Administration Core, works to increase transparency in reporting and reproducibility of research findings (M3.C) and to make Knight ADRC datasets widely available (M3.A).

C.4.4. The Neuropathology Core, in collaboration with the Administration Core, enables access to Knight ADRC biosamples (M3.D) and, in collaboration with the Clinical Core, addresses vascular contributions to dementia (M22.A.1) and explores disease mechanisms across neurodegenerative disorders (M2.H).

C.4.5. The Outreach, Recruitment, and Engagement Core collaborates with Knight ADRC scientists, including Morris, to identify and evaluate best practices for recruitment and retention of participants (M12.H) and develops novel community engagement methods (e.g., R13-funded 2018 national Workshop) for African Americans (M19.D.7). It also trains rural health professionals in the diagnosis and care of dementia (M16.A.3).

C.4.6. The Biomarker Core, in collaboration with the Genetics and High Throughput -Omics Core, generates cell-based models to identify mechanisms that underlie frontotemporal dementia (FTD) pathogenesis in *MAPT* mutation carriers (M.21.A.1) and in *GRN* mutation carriers (M.21.A.2, M21.A.4). Also in collaboration with the Genetics and High Throughput –Omics Core, it integrates genomic data with iPSC models (M2.G) and it develops improved protocols for relevant model systems (M4.F).

C.4.7. The Genetics and High Throughput -Omics Core, in collaboration with the Biomarker Core, identifies mechanisms of *GRN* mutations in FTD pathogenesis (M21.A.2) and integrates genomic data with iPSC models (M2.G). It also identifies multi-omic biomarker signatures (M9.B), explores single cell molecular profiling (M4.L), and leverages the power of human genetics to enable precision medicine research in AD (M4.K).

C.4.8. The REC expands existing and creates new integrative training programs for junior neuroscience and behavioral trainees (predoc, postdoc, junior faculty); implements cross-disciplinary training programs; and establishes career development programs to develop a new ADRD workforce (M4.J).

C.5. The Memory Diagnostic Center (MDC): Established in 1988 by Morris for his clinical dementia practice, the MDC now is the faculty outpatient practice for 11 physicians (including Morris, Holtzman, Bateman, Snider, Ghoshal, Musiek, Day, and McDade) and one nurse practitioner. Over 1,000 new patients with memory concerns, as well as ~1600 return patients, are seen yearly in the MDC. The MDC patients represent the full spectrum of ADRD and a wide spectrum of severity (i.e., from CDR 0.5 to CDR 3). Patients with very mild/mild symptomatic AD are also referred to Knight ADRC Clinical Core to determine eligibility for participation; currently 27 MDC patients are also Knight ADRC participants. Since April 2017, patients and their families can provide informed consent to permit their clinical data (including demographics, psychometric test scores, and CDR) to be entered into the MDC Data Repository. The Repository then can be accessed by investigators (after obtaining IRB approval and submitting a request to the MDC Director, Joy Snider, MD, PhD) to identify patients who may quality for specific research protocols. The Repository now contains data on 5,456 patients; 8 studies have enrolled MDC patients in their studies.

C.6. Succession Planning. Although remaining fully engaged in all aspects of the Knight ADRC and its affiliated studies, Morris is planning to ensure the future viability of the programs. Morris successfully transitioned leadership of the DIAN study to Dr. Bateman in 2015. Currently DIAN's Clinical Core Leader, Morris will transition Core leadership to Eric McDade, DO, in the next funding period for DIAN. Morris will transition leadership of the Knight ADRC to Dr. Holtzman in its next funding period, when Dr. Holtzman's Departmental and national leadership responsibilities (e.g. ANA) permit. Morris also transitioned the directorship of MDC to Dr. Snider in 2013. Morris is mentoring several junior faculty (e.g., Gregg Day, Lenise Cummings-Vaughn, and others) and, when they become established (i.e., Associate Professor), he will be able to transition leadership of the Knight ADRC Clinical Core to the individuals who are most appropriate for the role.

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