REQUEST FOR LETTERS OF INTENT TO SUBMIT PROPOSALS
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)
Letters of Intent (LOI) due Dec 31, 2020 (late submissions will be received and reviewed)
Send 2-page LOI to ADNIRFP@UCSF.edu

SUMMARY: This is a request for 2-page Letters of Intent to submit proposals concerning biomarkers or other assessment tools to the Alzheimer's Disease Neuroimaging Initiative (ADNI). Proposals concerning PET ligands for AD, fluid biomarkers for AD, and digital assessments including cognitive testing for AD are of particular interest, but an LOI for any assessment in other areas is welcome. Send LOI to ADNIRFP@UCSF.edu and all questions should be directed to the same email address.

INTRODUCTION: ADNI, founded in 2004, is a large multicenter public/private partnership grant funded by the National Institute on Aging, industry, and non-profit foundations. The grant is awarded to the Northern California Institute for Research and Education (NCIRE) in San Francisco. The Principal Investigator is Michael W Weiner MD. The goal of ADNI is to validate and standardize biomarkers for Alzheimer disease (AD) clinical trials. ADNI has enrolled over 2000 participants who have been followed longitudinally. ADNI makes all data and samples publicly available, resulting in over 2300 publications. The ADNI leadership is now planning a renewal of its NIA grant which will be due in September 2021. The planning process has been initiated. The ADNI leadership is interested in receiving proposals from industry, non-profit, and academic organizations who have biomarkers (especially PET ligands, fluid biomarker assays, digital biomarkers/cognitive testing etc.) and other assessment tools which could be used in the next phase of ADNI which would begin August 2022. Letters of Intent (LOI) are due Dec 31, 2020 (LOIs after that date may be considered), but much earlier submissions are very strongly encouraged. Send LOI to ADNIRFP@UCSF.edu and all questions should be directed to the same email address.

BACKGROUND OF ADNI (see adni.loni.usc.edu for more details):
ADNI was founded in 2004 in response to the emerging development of disease modifying treatments for AD, in contrast to the previously developed "cognitive enhancing" therapies, which were not designed to modify disease progression. It was generally accepted, in order to monitor progression of disease pathology, and to demonstrate that treatments slowed disease progression, that direct measurement of AD pathology was required. Therefore, there was a need to validate and standardize biomarkers (in contrast to clinical/neuropsychological evaluations) which detected AD pathology. Since its founding, ADNI has included patients with dementia thought to be due to AD, patients with mild cognitive impairment (MCI) and cognitively normal controls. Initially ADNI included MRI (various sequences), FDG PET, and cerebrospinal fluid (CSF) (from lumbar puncture) measurements, in addition to clinical assessments, neuropsychological tests, genetic assessments, and banking of plasma/serum. Later amyloid PET, tau PET, and collection of brain tissue from autopsy for pathology have been added. At home unsupervised cognitive testing has been added. Over 2000 participants have been enrolled at 60 sites across the USA and Canada and are followed annually. All clinical, cognitive, and biomarker results are available to any scientist in the world who requests the

data (request data at http://adni.loni.usc.edu/data-samples/access-data/). Over 2500 publications have used ADNI data. The CSF, plasma, serum, genetic, and peripheral cells have been banked and samples can be requested using procedures described on http://adni.loni.usc.edu/data-samples/access-data/**.**
The major accomplishment of ADNI is that ADNI data has been widely used by industry and academic groups to design and statistical power AD clinical trials. Additionally, ADNI has validated "amyloid β (Aβ) phenotyping" using amyloid PET and CSF measurements of Aβ. Such phenotyping has led to new diagnostic criteria for AD which are based on biomarker evidence of pathology. These have replaced previous criteria based on clinical signs and symptoms, which are both insensitive and non-specific. Longitudinal tau PET is now being validated. ADNI CSF, plasma/serum samples are being used to validate measurements of Aβ, tau/phosphorylated tau, neurofilament light chain, and other plasma markers, including proteomic assays. Finally, ADNI has been a successful model for public-private partnerships and many other multisite projects in the neurodegeneration field have been modeled on ADNI (DIAN, LEADS, PPMI and others).

The current ADNI project, termed ADNI3 ends Aug 31. 2022. A renewal submission is planned to be submitted in September 2021. The ADNI team is now engaged in planning design of the ADNI grant renewal. The planning process will come to an end in the Summer of 2021 when grant preparation begins. Because of the competitive nature of biomarkers, and other assessment methods for AD, neurodegeneration, cognition and dementia, ADNI is requesting short Letters of Intent (LOI) to submit Request for Proposals (more details below) to ADNIRFP@ucsf.edu as soon as possible. Although LOIs may be submitted on any topic relevant to ADNI, ADNI is specifically requesting LOIs concerning: 1) PET Ligands (especially for Aβ and tau), 2) plasma and CSF analysis (especially for Aβ, tau, phosphorylated tau, neurofilament light chain, as well as alpha synuclein and TDP 43, and others), and 3) digital biomarkers which can be used in-clinic and/or at home including mobile devices. More details on these 3 categories are explained below.

Please submit your letter no later than December 31, 2020, much earlier if possible. Please limit letters to 2 pages and describe the resource clearly so that we may evaluate its relevance to ADNI. Be sure to indicate (1) the process (e.g. brain proteins, plasma analytes, cognition/function) it will measure (2) the method used (3) the stage of development, including high impact results and relevant publications (4) confidentiality/intellectual property limitations. Based on the letters, a subgroup of applicants will be invited to submit more detailed proposals. A variety of factors will be considered by the ADNI leadership during the evaluation process. These factors will include: 1) demonstrated scientific value to detect AD and related pathology 2) availability for all clinic sites and participants in ADNI 3) cost to ADNI and other factors. The final decisions will be made by ADNI leadership.

PET LIGANDS

Types of ligands under consideration for ADNI4: We are specifically interested in PET radiopharmaceuticals that have been established for describing the phenotypes of participants according to the A/T/N biomarker framework. Thus, tracers of β-amyloid and pathological tau

are our primary area of interest. We also recognize that tracers for synaptic density and neuroinflammation may be useful in describing other key pathological processes in Alzheimer's disease pathogenesis and we are open to expressions of interest in providing these radiopharmaceuticals as well. There may also be other processes that we have not considered, and we are open to all letters of intent. The details of evaluation and selection will be released in coming months, but will entail review of proposals by an expert committee with a view towards selecting tracers that are scientifically well validated, have finalized and efficient radio-syntheses, can be provided to all (or a large majority) of ADNI sites and have a low cost. We are willing to consider more than 1 tracer in each category as final choices. The final decision will be made by the ADNI executive committee after expert review.

FLUID BIOMARKERS:

Types of CSF and plasma biomarkers under consideration for ADNI 4: Core analytes for CSF and plasma such as tau phosphorylated at several different sites including threonine 181 (p-tau 181) and, possibly, threonine 217 (p-tau 217), Aβ 40 and 42, as well as ratios of these analytes, and NfL. Proposals will be considered on other potentially informative tau and Aβ species as well as other analytes such as neurogranin, and other candidate markers of synaptic integrity; markers of glial dysfunction; markers of neuroinflammation, bile acids and other metabolomics groups of analytes, and numerous other candidate biomarkers that have emerged from large automated screens and proteomics platforms or others.

DIGITAL BIOMARKERS

With the advent of ADNI3 computerized cognitive testing was formally added to the program. The computerized testing was conducted through a dedicated website on the internet that was initially administered under supervision during an in-clinic study visit and was then accessed remotely by the participants without supervision. Collection of this data allowed for both cross-sectional analysis as well as longitudinal changes over the course of ADNI participation. Types of digital biomarkers under consideration for ADNI 4 will include paradigms that can similarly be administered both at the clinical site but with a stress on remote and unsupervised administration. The technology is not just limited to personal computers and tablets connecting to the internet but all applications that can be run on personal devices such as smart phones, smart watches and other similar devices. While the primary focus is on assessing the state and changes in cognition and executive function that may be accomplished through the computerization of standard paradigms, other domains and strategies are encouraged that will assess and quantify skills that will impact or reflect real-life functions, including physical activity/movement, and therefore quality of life. Both active "testing" as well as passive collection of activities and function, especially in the home environment are encouraged. LOI's from academic and commercial organizations will be considered as new biomarker tools to be included in ADNI4.

CONCLUSION: The ADNI leadership is interested in receiving proposals from industry, non-profit, and academic organizations who have biomarkers (e.g. PET ligands, fluid biomarker assays, digital biomarkers etc.) which could be used in ADNI4. Two-page Letters of Intent (LOI)

should be sent as soon as possible to be considered. Send LOI to ADNIRFP@UCSF.edu as soon as possible and questions should be directed to the same address.