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Major new research study to demonstrate value of PET scans in Alzheimer's disease diagnosis

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A new four-year research study, with an estimated budget of $100 million, was announced today by the Alzheimer's Association and the American College of Radiology (ACR). The Imaging Dementia - Evidence for Amyloid Scanning (IDEAS) Study will determine the clinical usefulness and value in diagnosing Alzheimer's and other dementias in certain situations of a brain positron emission tomography (PET) scan that detects a core feature of Alzheimer's disease.

The IDEAS Study will assess the impact of brain amyloid PET imaging on a variety of patient outcomes. The study protocol received approval with requirements by the Centers for Medicare & Medicaid Services (CMS). Participating providers will be reimbursed for the PET scans under the CMS Coverage with Evidence Development (CED) policy that requires research study participation as a condition of Medicare payment.

IDEAS is led by the Alzheimer's Association and managed by the ACR and American College of Radiology Imaging Network (ACRIN).

Why the IDEAS Study is NeededTwo abnormal structures called plaques and tangles are prime suspects in damaging and killing nerve cells in Alzheimer's. The plaques are deposits of a protein fragment called amyloid-beta that build up in the spaces between nerve cells. Amyloid PET imaging represents a potential major advance in the clinical

assessment of people with cognitive impairment. The technology makes amyloid plaques light up on a brain PET scan, enabling for the first time accurate detection of plaques in living people.

"The purpose of the IDEAS Study is to examine how brain imaging, specifically an amyloid PET scan, helps guide doctors in diagnosing and treating Alzheimer's and other dementias in cases where the cause of cognitive impairment is difficult to diagnose," said Gil D. Rabinovici, M.D., IDEAS Study Chair and Associate Professor of Neurology at the University of California, San Francisco. "We believe the study will show that, in diagnostically uncertain cases, knowledge of amyloid status will lead to significant changes in patient management - such as earlier counseling and prescription of more appropriate drugs - that will translate into improved long-term outcomes."

The IDEAS Study was developed in response to the 2013 CMS National Coverage Decision (NCD) on amyloid PET imaging in dementia and neurodegenerative disease (CAG-00431N) not cover the scans because "the evidence is insufficient to conclude that the use of positron emission tomography (PET) amyloid-beta (Aβ) imaging is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of ... Medicare beneficiaries with dementia or neurodegenerative disease."

CMS questioned the ability of PET amyloid imaging to lead to improved health outcomes, such as: avoidance of futile treatment or tests, improving or slowing the decline of quality of life, and survival. However, CMS did find sufficient evidence that the use of PET Aβ imaging is promising: (1) to exclude Alzheimer's in narrowly defined and clinically difficult diagnoses, and (2) to enrich clinical trials seeking better treatments or prevention strategies for Alzheimer's. Under the NCD, Medicare will provide coverage for one amyloid PET scan per patient enrolled in an approved clinical study.

"I am confident that, at the end of this study, we will have amassed sufficient data to assess whether amyloid imaging has a positive impact on patient outcomes leading to expansion of beneficiary access to this important procedure beyond the IDEAS Study," said Maria Carrillo, Ph.D., a co-chair of the IDEAS Study and Chief Science Officer at the Alzheimer's Association.

The IDEAS Study in More Detail

Amyloid PET imaging alone does not establish a diagnosis of Alzheimer's disease, but must be considered in the context of the person's medical history, physical examination, and cognitive testing. To guide clinicians on how best to apply amyloid PET in the clinical evaluation of people with cognitive decline, a working group convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) developed appropriate use criteria (AUC) for brain amyloid PET scans.

The AUC indicate that amyloid PET should only be considered in patients with clear, measurable cognitive deficits when there is substantial diagnostic uncertainty after a comprehensive evaluation by a dementia specialist. According to AUC, amyloid PET may have greatest value in patients with either: (1) progressive, unexplained mild cognitive impairment (MCI); or (2) dementia of uncertain cause due to atypical or mixed symptoms, or unusually early age-of-onset.

A total of 18,488 Medicare beneficiaries age 65 and older meeting AUC will be enrolled over 24 months at roughly 200 sites throughout the United States. Study participants will be recruited into one of two sub-groups: (1) progressive, unexplained MCI, and (2) dementia of uncertain cause.

All referrals to the study and for amyloid PET will come from dementia

specialists, defined by the Alzheimer's Association and SNMMI as "physicians trained and board-certified in neurology, psychiatry, or geriatric medicine who devote a substantial proportion of patient contact time to the evaluation and care of adults with acquired cognitive impairment or dementia, including probable or suspected Alzheimer's disease." Dementia specialists will be recruited through societies such as the International Association of Gerontology and Geriatrics, American Academy of Neurology, American Society of Neuroradiology; plus clinician outreach through psychiatrists, members of the Alzheimer's Association, and news media outreach.

The IDEAS Study will address two specific aims:

- Assess the impact of amyloid PET on the management of patients meeting Appropriate Use Criteria.
- Assess the impact of amyloid PET over 12 months on major medical outcomes such as hospital admissions and emergency room visits in patients enrolled in the study compared to matched patients not in the study.

Aim 1 investigates the impact of amyloid PET on short-term patient management by comparing pre-PET intended management to post-PET actual management recorded 90 days after the scan by the referring physician. Examples of changes in management include: use of Alzheimer's drug therapy, other drug therapy, and counseling about safety and future planning.

Aim 2 utilizes Medicare claims data to compare medical outcomes at 12 months for patients enrolled in the study with a matched control cohort of patients who have never undergone amyloid PET imaging. The primary objective will be to determine if amyloid PET testing in the amyloid PET-known cohort of patients is associated with a significant reduction in major medical outcomes, including hospitalizations and

emergency room visits. The study will also investigate how the scans impact use of health care resources and services.

"In pursuing these aims, we also will generate valuable data on clinical utility that will inform future use of brain amyloid PET as a diagnostic tool, and establish a large group of patients who have had amyloid PET and can serve as a study population to address future research questions," Rabinovici said.

IDEAS Study Leadership

The IDEAS Study Chair is Gil D. Rabinovici, M.D., Associate Professor of Neurology at the University of California, San Francisco, a behavioral neurologist with research expertise in amyloid PET. The leadership team includes Bruce E. Hillner, M.D., from Virginia Commonwealth University and Barry A. Siegel, M.D., from Washington University, the chair and co-chair, respectively, of the National Oncologic PET Registry (NOPR), one of the most influential registries developed in response to the CMS CED requirements. Data management and statistical analyses will be managed by the American College of Radiology/American College of Radiology Imaging Network and Brown University, which were the data hosts for statistical evaluations in NOPR under the leadership of Constantine Gatsonis, Ph.D. The study leadership team further includes Rachel Whitmer, Ph.D., a Senior Scientist and Epidemiologist at Kaiser Permanente Division of Research and an expert on population-based studies of dementia risk factors and outcomes. The IDEAS Study protocol development has been coordinated by the Alzheimer's Association, under the leadership of Maria Carrillo, Ph.D., Chief Science Officer, and the ACR.

The total budget for the study is estimated at $100 million over four years. CMS will provide reimbursement to participating PET facilities for the costs associated with the PET scans. Additional funding to

support the research infrastructure and analysis will be raised from philanthropists, industry and other key stakeholders.

The U.S. Food and Drug Administration has approved three amyloid PET imaging radiopharmaceuticals for clinical use: F-18 florbetapir (Amyvid™), F-18 flutemetamol (Vizamyl™), and F-18 florbetaben (Neuraceq™). The manufacturers of these radiopharmaceuticals have been engaged in supporting the study design and implementation through the Medical Imaging & Technology Alliance.

Why An Accurate Alzheimer's Disease Diagnosis Is So Important

Accurately diagnosing the cause of cognitive impairment and dementia helps direct therapy and leads to a care plan that improves patient safety and minimizes the risk of preventable complications. Establishing the diagnosis in the early stages of cognitive impairment enables people to participate in care planning and legal and financial planning, while they are still able, and thus promotes patient autonomy. Studies suggest that most people seeking a cognitive evaluation want to be informed if Alzheimer's is the cause of their symptoms. Receiving a definitive diagnosis often has a positive psychological impact on most people who are experiencing memory and thinking symptoms and their caregivers.

Nonetheless, the Alzheimer's Association's 2015 Alzheimer's Disease Facts and Figures report, released in March, found that only 45 percent of people with Alzheimer's disease or their caregivers say they were told the diagnosis by their doctor. With a diagnosis, people can better understand the changes they are experiencing, maximize their quality of life, and play an active role in planning for the future.

The diagnosis of Alzheimer's and other dementias is currently based on

the person's history, physical examination, and cognitive testing. The limitations of this approach are increasingly evident, and have negative implications for patient care. For example, studies suggest that the majority of eligible patients do not receive approved Alzheimer's drugs, which have been shown to improve symptoms in dementia due to Alzheimer's in some people for a period of time. Conversely, research shows that Alzheimer's drugs are regularly used off-label in people with non-Alzheimer's causes of dementia. For these people, use of these medications is often associated with adverse outcomes.

Lack of diagnostic accuracy also represents a barrier to developing and testing drugs. In two recent Phase III trials of immunotherapies targeting amyloid-beta, approximately 20% of patients clinically diagnosed with mild to moderate Alzheimer's did not show evidence of amyloid on PET scans, and thus lacked the primary drug target.

Provided by Alzheimer's Association