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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2017

ALZHEIMER'S ASSOCIATION LAUNCHES $20 MILLION LIFESTYLE INTERVENTION TRIAL IN THE U.S. TO PREVENT COGNITIVE DECLINE

– Results from 4,000 Participants re: Impact of Brain Amyloid Imaging on Medical Management –
– Possible Blood Test for Amyloid –

LONDON, July 19, 2017 – The Alzheimer's Association today announced the launch of a $20 million U.S. two-year clinical trial to test the ability of a multi-dimensional lifestyle intervention to prevent cognitive decline and dementia in 2,500 older adults with no current cognitive symptoms but who are at increased risk for later cognitive decline. The announcement was made at the 2017 Alzheimer's Association International Conference (AAIC 2017) in London.

The large U.S. study to PrOtect through a lifestyle INTErvention to Reduce risk (US POINTER) will include physical exercise, nutritional counseling and modification, cognitive and social stimulation, and improved self-management of medical conditions. Recruiting for the study will begin in 2018.

At AAIC 2014, Miia Kivipelto, M.D., Ph.D., Professor at the Karolinska Institutet, Sweden and the National Institute for Health and Welfare, Helsinki, Finland, and colleagues reported on the results of the FINGER Study – the first randomized controlled trial showing that it is possible to prevent cognitive decline using a multi-domain lifestyle intervention among older at-risk individuals. The results highlighted the value of addressing multiple dementia risk factors as a strategy to protect brain health. The FINGER model is now being replicated in the United States, Europe, Singapore, and Australia – including people from a variety of geographical and cultural backgrounds.

"We now can effectively prevent and treat heart disease with a combination of drugs and lifestyle. The same is true with some cancers; the same with HIV/AIDS. The same may also be true for Alzheimer's disease and other dementias in the not too distant future," said Maria C. Carrillo, PhD, Alzheimer's Association Chief Science Officer.

"We must test all options to treat and prevent this horrible disease. We must find the answers for the millions dying with Alzheimer's and their families, and the tens of millions more who will become affected if we do not act now. The Alzheimer's Association is extremely proud to launch this clinical trial with our scientific partners," Carrillo said.

Also announced today at AAIC 2017:

- Interim results of the IDEAS Study, which is testing the impact on medical management of brain PET scans to detect amyloid protein. Amyloid forms the hallmark brain plaques of Alzheimer's disease.
- A possible blood marker for amyloid build up in the brain.
- New insights into how amyloid and tau proteins spread through the brains of people with Alzheimer's. Abnormal tau forms brain tangles – the other hallmark lesion of Alzheimer's.

U.S. study to PrOtect through a lifestyle INTErvention to Reduce risk (US POINTER)

Increasing age is the greatest risk factor for Alzheimer's disease. With the aging of the global population – and the slow progress of developing and testing drug treatments – prevention is pivotal in managing the inexorable rise in global cases of Alzheimer's and other dementias.

In 2014, a large-scale two-year study in Finland in healthy older adults at increased risk of cognitive decline and dementia (the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability, or FINGER Study) found that a two-year combination therapy involving physical exercise, nutrition, cognitive stimulation, and self-monitoring of heart health risk factors had a protective effect on cognitive function. These results were first reported at AAIC 2014 in Copenhagen.

According to Co-Principal Investigator Laura Baker, PhD, of the Wake Forest School of Medicine, Winston-Salem, North Carolina, the U.S. study to PrOtect through a lifestyle INTErvention to Reduce risk (US POINTER) is modeled on the FINGER study. It will test whether two years of a combined intervention that includes physical exercise, nutritional counseling and modification, cognitive and social stimulation, and improved self-management of medical co-morbidities benefits cognitive function in older adults at increased risk of cognitive decline and dementia. The comparison group will receive health education and support through in-person group meetings on health- and aging-related topics, and annual feedback on laboratory tests.

Starting in 2018, 2,500 study participants 60-79 years old will be identified using a medical record search to select those with medical conditions that have been linked to an increased risk for dementia (e.g., hypertension and other cardiovascular events, elevated blood sugar). Information about family history of Alzheimer's, physical activity level, and current cognitive status and mood will be collected in follow-up interviews to further identify eligible participants. Local Alzheimer's Association offices nationwide will participate in intervention delivery. National partnerships will be developed with community-based organizations to deliver the exercise, nutrition, social and medical aspects of the intervention.

The success of the intervention will be evaluated based on two-year change in a global measure of cognitive function focused on short-term memory, attention and concentration.

"As of now, there are no approved medications that have produced results similar to the FINGER Study. There is a pressing need to test the effectiveness of a multicomponent lifestyle intervention in larger and more diverse populations, such as the United States," said Baker. "The lifestyle intervention in US POINTER is an important multi-dimensional strategy to protect brain health and potentially reduce risk of dementia."

An update on FINGER and overviews of the Singapore (SINGER) and Australia (Maintain Your Brain) prevention studies will also be reported at AAIC 2017. The worldwide effort, collectively referred to as WW-FINGERS, supports a collaborative network of trials and experienced investigators to facilitate harmonization of research methods, and sharing of experiences and data for maximum global scientific impact.

Clinical Impact of Brain Amyloid PET Scans – Interim Results from the IDEAS Study

Launched in 2016, the four-year Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study is evaluating the impact of brain amyloid PET scans on patient management and health outcomes. Participants are more than 18,000 Medicare beneficiaries age 65+ with mild cognitive impairment (MCI) or atypical dementia who meet published Appropriate Use Criteria (AUC) for clinical amyloid PET. Before brain amyloid PET scans – which detect amyloid plaques, a core feature of Alzheimer's – amyloid plaques could be seen only during autopsies, making it much harder to give living patients a definitive diagnosis.

At AAIC 2017, Principal Investigator Gil Rabinovici, MD, of the Memory and Aging Center, University of California, San Francisco, and colleagues reported early results from IDEAS assessing changes in patient management in the first 3,979 participants for whom case report forms were completed by participating dementia specialists both before and 90 days after the PET scans.

The pre-PET form documented the specialist's management plan assuming no access to amyloid PET; the post-PET form recorded the medical management plan approximately 90 days after receiving results from a brain amyloid PET with an FDA-approved beta-amyloid imaging agent.

The researchers measured the rate of change between pre- and post-PET medical management, including one or more of: Alzheimer's disease drug therapy, other drug therapy, and counseling about safety and future planning. Participants' median age was 75 (range: 65-95); 64.4% were diagnosed with MCI, 35.6% met criteria for dementia. The most common suspected cause of cognitive impairment prior to PET was Alzheimer's disease (76.3%). Rates of amyloid PET positivity were 54.3% in MCI and 70.5% in dementia.

Changes in medical management were seen in 67.8% of MCI patients (47.8% change in AD drugs, 36.0% change in other drugs, 23.9% changes in counseling), and in 65.9% of dementia patients (47.7% change in AD drugs, 32.2% change in other drugs, 15.3% change in counseling). Amyloid PET scans also reduced the need for additional diagnostic testing such as neuropsychological testing (from 26.3% recommended pre-PET to 11.0% recommended post-PET) and spinal fluid testing (from 10.5% to 1.0%).

"Our original hypothesis was that having amyloid PET scan results would change medical management in 30 percent of cases," Rabinovici said. "Our interim results suggest we are well on track to see an effect of at least that magnitude, and perhaps greater, when the final results are available."

"We look forward to reporting the results from the full study population. We are very grateful to the Centers for Medicare & Medicaid Services for their support of the IDEAS Study as our results indicate that access to this technology is making a real difference in the care of patients," Rabinovici added.

The IDEAS Study is led by the Alzheimer's Association and managed by the American College of Radiology.

The IDEAS Study was developed in response to CMS' 2013 National Coverage Decision (NCD) on amyloid PET imaging in dementia and neurodegenerative disease (CAG-00431N) not to 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." Under the NCD, Medicare will provide coverage for one amyloid PET scan per patient enrolled in an approved clinical study.

A working group convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) developed 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 Blood Biomarker for Amyloid Plaques?

There is substantial evidence implicating amyloid-beta in the cause and/or progression of Alzheimer's disease. Currently, a spinal tap or PET scan can detect deposition of amyloid in the brain, which precedes and increases the risk of progression to Alzheimer's disease dementia. However, due to the invasiveness of a spinal tap and the radioactivity, limited availability and cost of PET scans, there is an urgent need for a simpler, more practical test for amyloid deposition, such as a blood test.

In order to investigate a blood-based amyloid biomarker, Randall Bateman, MD, and scientists at Washington University School of Medicine in St. Louis adapted their previously reported Stable Isotope Label Kinetics (SILK) method to measure amyloid in the blood – how fast it is created and how fast it is cleared away.

Participants were 41 older adults either with or without amyloidosis in the brain; they had either clinically diagnosed late-onset Alzheimer's or were cognitively normal age-matched controls. All participants had brain PET amyloid imaging and/or cerebrospinal fluid (CSF) amyloid measures to detect brain amyloidosis. Blood sampling was conducted over 24 hours, and analyzed in a blinded fashion so researchers didn't know which samples were from amyloid positive or amyloid negative people.

The scientists found the longer, stickier form of amyloid (known as Aβ42) was created and removed significantly faster in amyloid positive participants compared to amyloid negative participants. The findings were similar to prior studies done in CSF, suggesting that the amyloid levels detected in blood can accurately reflect the amyloid buildup in the brain. Additional results of a larger validation study will also be reported at AAIC 2017.

"These findings are important because they support the idea that blood amyloid interacts with and is derived from the brain," Bateman said. "We're excited because the results also suggest that blood-derived amyloid-beta may be useful as a rapid and inexpensive screening test for brain amyloidosis, and may be able to identify people who are at higher risk of Alzheimer's disease very early in the process."

"Having a simple and inexpensive blood test for screening is likely to greatly accelerate clinical trials to find Alzheimer's drugs. And, it could facilitate widespread treatment when effective anti-amyloid therapeutics are developed," Bateman added. "We envision that one day soon, as part of a regular screening for cholesterol and blood pressure, a person may also get a blood test to find out if the amyloid protein is building up in the brain, and then go on specific treatments to prevent the onset of Alzheimer's disease dementia. This would be similar to the already successful approach of screening for and treating high cholesterol to reduce the risk of heart attacks and strokes."

This research was supported by an Alzheimer's Association Zenith award grant and an NIH R01 study.

Amyloid and Tau Spreading Pathways in the Brain, Correlated with Genetics

The ability to employ advanced imaging technology to "see" both of the hallmark proteins of Alzheimer's (amyloid and tau) in the living brain is a significant recent advance in the field. It may prove to be transformational not only in our understanding of the disease and its progression but also in its potential to accelerate drug discovery.

According to Jorge Sepulcre, MD, PhD, of Massachusetts General Hospital and Harvard Medical School, Boston, understanding the "spreading" phenomenon of abnormal tau and amyloid-beta proteins in the brain is critical to knowing what is causing the devastating cell damage and relentless symptoms of people with Alzheimer's.

Sepulcre and colleagues developed a novel imaging approach to investigate the spreading pathways of tau and amyloid deposits over time, as well as their genetic vulnerabilities, in a longitudinal sample of elderly participants in the Harvard Aging Brain Study. Eighty-eight (88) study participants, average age about 76, were divided into two independent samples: (1) a cross-sectional sample of 69 people; and (2) a 1-2 year follow-up longitudinal sample of 19 subjects.

The researchers found that tau and amyloid appear to accumulate along distinctive pathways in the brain; the same communication pathways, or neural networks, we use for daily brain function. According to their findings, tau - which we know starts in the middle of the brain memory center - spreads forward and out toward the front of the brain. Amyloid, which starts in the back of the brain, spreads further back and outward from the middle. Specifically:

- Medial/inferior temporal lobe areas project pathways of Tau-spreading toward anterior pole, lateral and posteriomedial temporal cortex, and orbitofrontal cortex.
- Posterior cingulate cortex spreads Aβ toward surrounding areas and lateral parietal lobe.

The scientists discovered that 354 genes were significantly associated with the tau spreading pathway, including the MAPT gene, which was previously associated with Alzheimer's disease risk. They also found 216 genes, including the CLU gene, significantly associated with the amyloid pathway. Additional analysis characterized the tau spreading genetic profile as "axon-related" and the amyloid-spreading genetic profile as "dendrite-related". APOE, the gene with the highest impact on Alzheimer's risk, was found to be the most central gene linking tau- and amyloid-spreading pathways.

"Our results reported at AAIC 2017 suggest that tau and amyloid advance through different brain systems over time," Sepulcre said. "We also discovered certain genetic traits that may confer tau or amyloid vulnerability in the brain."

"The findings may improve our ability to track responses to potential therapeutic interventions in the future," Sepulcre added. "In addition, when more effective drug therapies become available, these results may help doctors determine which patients should get which therapies, and the optimum time to take them."

About Alzheimer's Association International Conference (AAIC)
The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2017 home page: www.alz.org/aaic/
AAIC 2017 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer's Association
The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call +1 800.272.3900.

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- Laura D. Baker, PhD, et al. U.S. Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (US-FINGER). (Funder: Alzheimer's Association)
- Gil D Rabinovici, MD, et al. Impact of Amyloid PET on Patient Management: Early Results from the IDEAS Study. (Funder(s): U.S. Center for Medicare and Medicaid Services, Alzheimer's Association, Eli Lilly, GE Healthcare, Piramal)
- Randall J Bateman, MD, et al. Concentrations and Stable Isotope Label Kinetics of Human Plasma Amyloid Beta. (Funder(s): U.S. National Institutes of Health, Alzheimer's Association)
- Jorge Sepulcre, MD, PhD, et al. In Vivo spreading Pathways of Tau and Amyloid Accumulation and Its Genetic Underpinnings. (Funder(s): U.S. National Institutes of Health, Alzheimer's Association)

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Public Health and Psychosocial: Global Dementia Prevention Initiative: Applicability of the Multi-Domain Interventions
Featured Research Session F4-09, Wednesday, July 19, 2017: 4:15-5:45 PM

Session Overview: Prevention is pivotal in managing the dementia epidemic globally. Given the multifactorial etiology of dementia and late-onset AD, multi-domain interventions targeting several risk factors are most likely to be effective. Three European countries have completed pioneering multi-domain prevention RCTs in community-dwelling seniors: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER); the French Multidomain Alzheimer Preventive Trial (MAPT); the Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA). These studies address key methodological issues underlying the successful delivery of cost-effective preventive interventions. This requires integrated approaches targeting risk factors shared by chronic disorders common in older age, the definition of accessible and sustainable strategies for populations with different geographical, economic and cultural settings.

FINGER is the first large, long-term RCT indicating that a multi-domain intervention with exercise, diet, cognitive and social stimulation and management of vascular/metabolic risk factors may benefit cognition in subjects at risk of dementia. FINGER represents a pragmatic model, now being tested in diverse population-based settings (Europe, Singapore, USA, Australia).

The Global Dementia Prevention Initiative (GDPI) is an interdisciplinary network, sharing experiences, ideas and data, and planning joint initiatives focusing on cognitive impairment/dementia prevention. Overall goal is to generate robust evidence to define effective preventive approaches for various at-risk groups and settings. GDPI will facilitate synergistic use of data from several countries, creating a unique opportunity for rapid implementation of knowledge. The symposium will introduce the GDPI and ongoing/planned multi-domain preventative initiatives. New results, methodological issues, and potential impact and implementation will be discussed.

Abstract 19107 Proposal ID F4-09-01
From the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability to the Global Dementia Prevention Initiative: Applicability of Multi-Domain Interventions.

Miia Kivipelto, MD, PhD1,2,3,4 **(miia.kivipelto@ki.se)**, Francesca Mangialsche, MD PhD5, Tiia Ngandu, MD, PhD3, Alina Solomon, MD, PhD6, Jaakko Tuomilehto, MD, PhD7, Hilkka Soininen, PhD6 and For the FINGER study group, (1)Institute of Clinical Medicine/Neurology, University of Eastern Finland, Kuopio, Finland, (2)Karolinska Institutet, Stockholm, Sweden, (3)National Institute for Health and Welfare, Helsinki, Finland, (4)Karolinska Institutet-Stockholm University, Stockholm, Sweden, (5)Karolinska Institutet, Sweden, Sweden, (6)University of Eastern Finland, Kuopio, Finland, (7)Department of Chronic Disease Prevention, Helsinki, Finland

Background: Prevention can be pivotal in halting the expected worldwide increase of Alzheimer´s disease (AD) and dementia cases. Given the multifactorial etiology of dementia and late-onset AD, multi-domain interventions targeting several vascular and lifestyle-related risk factors are most likely to be effective. Successful preventative approaches should be cost-effective, accessible, feasible, and sustainable for populations with different geographical, economic and cultural settings. **Methods**: The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a pioneer multi-domain randomized controlled trial (RCT), where 1260 participants aged 60-77 years were recruited from the general population using the CAIDE Dementia Risk Score. Participants were randomized (1:1) either into a 2-year multi-domain intervention or the control group. The intervention included nutritional guidance, physical exercise, cognitive training and social activities, as well as management of vascular and metabolic risk factors. The control group received regular health advice. Primary outcome after 2 years was change in cognition (neuropsychological test battery, NTB z-score). **Results:** A significant beneficial intervention effect on overall cognitive performance and various cognitive domains was found, showing for the first time that a multi-domain intervention may benefit cognitive functions in older subjects at increased risk of dementia. Intervention benefited also secondary outcomes (Body Mass Index, diet, physical exercise). New results concerning quality of life, functional level, and other secondary outcomes will be presented, as well as the extended follow-up. FINGER represents a successful pragmatic model, which is now being tested in diverse population-based settings (Europe, Singapore, USA, Australia). Novel approaches include combination of lifestyle intervention with pharmacological intervention (e.g. Multimodal preventive trials for AD) and use of modern technology (e.g. Healthy Aging Through Internet Counselling in the Elderly). To promote

synergy across these studies and optimize efforts towards dementia prevention, we launched the Global Dementia Prevention Initiative (GDPI). GDPI is an interdisciplinary network, to share experiences, ideas and data, and plan joint initiatives focusing on cognitive impairment/dementia prevention. **Conclusions:** GDPI will facilitate synergistic use of data from several countries, creating a unique opportunity for rapid implementation of knowledge and definition of effective prevention programs for diverse populations.

Abstract# 19110 / Proposal ID F4-09-02
U.S. Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (US-FINGER)

Laura D. Baker, PhD1**(ldbaker@wakehealth.edu)**, Rachel A. Whitmer, PhD2, Miia Kivipelto, MD, PhD3,4, Heather M. Snyder, PhD5, Christopher P Chen, MD6, Mark A Espeland, PhD1, Rema Raman, PhD7,8, Kaycee M. Sink, MD, MAS9, Jeff D. Williamson, MD, MHS9 and Maria C. Carrillo, Ph.D.5
(1)Wake Forest School of Medicine, Winston-Salem, NC, USA, (2)Kaiser Permanente Division of Research, Oakland, CA, USA, (3)Karolinska Institutet, Stockholm, Sweden, (4)National Institute for Health and Welfare, Helsinki, Finland, (5)Alzheimer's Association, Chicago, IL, USA, (6)Yong Loo Lin School of Medicine, National University of Singapore, Kent Ridge, Singapore, (7)Alzheimer's Therapeutic Research Institute, San Diego, CA, USA, (8)University of Southern California, San Diego, CA, USA, (9)Wake Forest School of Medicine, Winston Salem, NC, USA

Background: Lifestyle interventions focused on combining healthy nutrition, physical activity, and social and intellectual challenge may represent a promising therapeutic strategy to protect brain health. The recent results of the population-based 2-year clinical trial, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), indicated that a multidomain intervention of physical activity, nutritional guidance, cognitive training, social activities and management of heart health risk factors slowed cognitive decline in healthy older adults at increased risk of cognitive decline. As yet, there are no pharmacological treatment options that can rival this effect. Thus, there is an urgent need to expand this work to test the generalizability, adaptability, and sustainability of their findings in diverse and global populations. **Methods:** The U.S. Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (US-FINGER) trial builds on lessons learned from FINGER and will test a 2-year multi-site and community-based multidomain intervention of physical activity, nutritional guidance, cognitive training and social activities, and management of medical co-morbidities in asymptomatic older adults aged 60-79 years. Study candidates will be identified through medical history to assess dementia risk using an algorithm that includes vascular and other established predictors. Family history of dementia and physical activity level will also be queried using follow-up questionnaires for those identified through the algorithm. A cognitive composite score focused on episodic memory and executive function will serve as the primary outcome. **Results:** An overview of the study design, target population and recruitment approach, interventions, outcomes, and implementation strategies for US-FINGER will be discussed. **Conclusions:** In the absence of other effective treatment options and in the wake of promising findings from FINGER, there is a pressing need to replicate FINGER in diverse and larger populations. US-FINGER hopes to expand the scientific footprint of the Finnish study and test the generalizability, adaptability, and sustainability of a multidomain behavioral intervention to effectively prevent cognitive decline and progression to Alzheimer's dementia.

Abstract 19111 Proposal ID F4-09-03
Singapore Intervention Study to Prevent Cognitive Impairment and Disability (SINGER) Initiative

Christopher Chen, FRCP1, Xin Xu, PhD2, Effie Chew, MD3, Christiani Jeyakumar Henry, PhD2 and Edward H. Koo, MD2, (1)Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, (2)National University of Singapore, Singapore, Singapore, (3)National University Hospital, Singapore, Singapore

Background: As the ageing population in the developing world increases, a concomitant rise in the incidence of dementia is expected with 71% of dementia cases projected to be in the developing world by 2040. Demographic changes in Asia will quadruple the prevalence of dementia in 2050 to an estimated 64.6 million people from 13.7 million cases in 2005. The prevalence of dementia in Singaporean epidemiological studies ranges from 2% to 6%. However, as age adjusted dementia prevalence rates are unlikely to differ between populations and since Singapore has a rapidly ageing population with 20% of the population aged 65 and above by the year 2030, the

prevalence of dementia in Singapore is expected to increase exponentially. Although Alzheimer's Disease (AD) may be the most common form of dementia, it is likely that vascular causes of dementia play an equally significant role in Singapore because of the high prevalence of cerebrovascular disease – one of the highest rates globally. Hence the results of the FINGER study may be of great importance and relevance to Asia in general and Singapore in particular. **Methods**: The SINGapore intervention study to prevEnt coGnitive impairment and disability (SINGER) initiative aims to initially develop pilot studies of culturally appropriate interventions based on FINGER so as to eventually undertake a large confirmatory study. **Results**: An overview of the study design, interventions, outcomes, and implementation strategies for SINGER will be discussed. **Conclusions**: There are challenges particularly in adapting dietary and cognitive interventions for Asian populations but novel approaches are required to address the challenge of preventing cognitive impairment in aging populations.

Abstract 19112 Proposal ID F4-09-04
Maximising Technology and Methodology for Internet Prevention of Cognitive Decline: The Maintain Your Brain Trial

Henry Brodaty, MD, DSc, FRACP, FRANZCP, Centre for Healthy Brain Ageing (CHeBa), Sydney, Australia; UNSW Sydney, Sydney, Australia and Maintain Your Brain Research Team

Background: The possibility of preventing or delaying cognitive decline and dementia non-pharmacologically is becoming a reality. Epidemiological studies have demonstrated environmental risk factors account for 30% of population attributable risk of Alzheimer's disease and that the incidence of dementia is declining. The FINGER study, a clinic based intervention, was the first RCT to provide proof of concept that attending to lifestyle and vascular factors protects against cognitive decline. The field is moving to internet delivery of intervention. We describe methodological challenges to conducting such interventions. **Methods**: Key considerations are: (1) Sample: Age is critical in choosing the target population. (2) Recruitment: How to engage and minimise bias. (3) Risk factors: Participants must have modifiable risk factors and so have possibility of improvement. Not all risk factor can be directly addressed online. (4) Interventions: How to engage participants initially, maintain their participation and ensure they follow recommendations over several years. Vascular risks can be handled indirectly through lifestyle changes and through participants' general practitioners. (5) Assessment: Online testing of most cognitive domains is available. Physical exercise can be monitored remotely and by self-report. Diet relies on self-report which can be enhanced with food diaries and setting goals. Online treatment for depression and anxiety has had impressive results. **Results**: Maintain Your Brain (MYB) is a multimodal RCT which will target 18,000 55-75 year olds – young enough to have less accumulated brain pathology but old enough to decline within a research timeframe. MYB is recruiting from the Australian Medicare list, a population-based cohort of persons who are computer connected and have at least two risk factors for dementia. MYB will provide four intervention modules - physical activity, diet, cognitive training and depression treatment - to address known modifiable risk factors for dementia. MYB addresses cardiovascular risks indirectly through these modules and with advice to consult participants' general practitioners. Pivotal to success is an interactive and friendly IT platform with back-up support as required. **Conclusions**: MYB will be the largest internet based prevention trial. Developing the program requires time, careful planning and consumer consultation.

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Abstract 19866 / Proposal ID DT-01-01
Developing Topic: Biomarkers
Oral session, Wednesday, July 19, 2017: 2:00–3:30 PM

Impact of Amyloid PET on Patient Management: Early Results from the IDEAS Study

Gil D Rabinovici, MD1(Gil.Rabinovici@ucsf.edu) Constantine Gatsonis, PhD2, Charles Apgar, MBA3, Ilana F Gareen, PhD2, Lucy Hanna, MS2, James Hendrix, PhD4, Bruce E Hillner, MD5, Cynthia Olson, MBA, MHS3, Justin Romanoff, MS2, Barry A Siegel, MD6, Rachel A. Whitmer, PhD7, Maria C. Carrillo, Ph.D.4 and on behalf of the IDEAS Study investigators
(1)Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA, (2)Dept. of Biostatistics, Brown University, Providence, RI, USA, (3)American College of Radiology Imaging Network, Philadelphia, PA, USA, (4)Alzheimer's Association, Chicago, IL, USA, (5)Dept. of Medicine, Virginia Commonwealth University, Richmond, VA, USA, (6)Dept. of Radiology, Washington University, St. Louis, MO, USA, (7)Kaiser Permanente Division of Research, Oakland, CA, USA

Background: The Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study is evaluating the impact of amyloid PET on patient management and health outcomes in ~18,500 Medicare beneficiaries age ≥ 65 with mild cognitive impairment (MCI) or atypical dementia who meet Appropriate Use Criteria (AUC) for clinical amyloid PET. Here we report early results assessing changes in patient management in the first 3,979 participants in whom case report forms (CRFs) were completed before and ~90 days after PET. This represents one-third of the planned enrollment for assessing impact on patient management. **Methods**: All patients were referred by dementia specialists implementing AUC. The pre-PET CRF documented the specialist's management plan assuming no access to amyloid PET, while the post-PET CRF recorded the implemented management plan approximately 90 days following PET with an FDA-approved beta-amyloid ligand. We measured the rate of change between pre- and post-PET management in a composite endpoint that includes one or more of the following: (1) Alzheimer's disease (AD) drug therapy, (2) other drug therapy, or (3) counseling about safety and future planning. **Results**: The median age of the cohort was 75 (range: 65-95), 50.7% were female, and 90.2% were White or Caucasian. 64.4% of patients were diagnosed with MCI, 35.6% met criteria for dementia. The most common suspected etiology for cognitive impairment prior to PET was AD (76.3%) followed by non-AD neurodegenerative disease (11.9%). Rates of amyloid PET positivity were 54.3% in MCI and 70.5% in dementia. Changes in the composite management endpoint were seen in 67.8% (95% CI: 66.0% - 69.6%) of MCI patients (47.8% change in AD drugs, 36.0% change in other drugs, 23.9% changes in counseling), and in 65.9% (95% CI: 63.4%-68.3%) of dementia patients (47.7% change in AD drugs, 32.2% change in other drugs, 15.3% change in counseling). Secondary management endpoints which showed > 10% pre to post-PET change in the overall population included: neuropsychological testing (17.3%), referrals to AD therapeutic trials (15.0%), and referrals for FDG-PET (13.2%) and MRI (10.2%). **Conclusions**: Early IDEAS Study data indicate that amyloid PET may have a substantial impact on patient management.

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Abstract #19667 / Proposal ID DT-01-03
Developing Topic: Biomarkers
Oral session, Wednesday, July 19, 2017: 2:00–3:30 PM

Concentrations and Stable Isotope Label Kinetics of Human Plasma Amyloid Beta

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Background: There is substantial evidence implicating amyloid-beta (Ab) in the molecular pathogenesis of AD1. Cerebrospinal fluid (CSF) Aβ is an established biomarker for detecting amyloidosis2 and risk of progression to dementia3. However, blood Aβ concentrations have correlated poorly with clinical AD4. Furthermore, Aβ amyloid binding positron emission tomography (PET) tracers have emerged as sensitive and specific signatures of amyloid deposition in the central nervous system (CNS)5. However, due to the invasiveness of CSF collection and the limited availability and cost of PET scans, there is an urgent need for a simpler, more practical Ab biomarker for CNS amyloid deposition. To investigate a plasma-based Ab biomarker, we adapted our previously reported Stable Isotope Label Kinetics (SILK) protocol6,7 to analyze the turnover kinetics and absolute amounts of Ab38, Ab40, and Ab42. **Methods:** As part of an Alzheimer's Association Zenith award grant and NIH R01 study (NS065667), 118 SILK studies were completed with either clinically diagnosed AD or cognitively normal age-matched control participants at Washington University School of Medicine. All participants had Aβ amyloid imaging by PIB PET and/or CSF Aβ measures to detect CNS amyloidosis. Participants were given a bolus of 13C6-leucine label followed by blood sampling over 24 hours. Blood samples were immediately processed to plasma and analyzed in a blinded fashion. Ab isoforms were immunoprecipitated with an anti-Ab antibody and analyzed on a high resolution liquid chromatography mass spectrometer6. **Results:** We found shorter half-life of Aβ38 in all participants, and Aβ42/40 fractional turnover rate ratios trended towards faster turnover in amyloid positive participants similar to, but of lesser magnitude compared to kinetics measured in CSF7. We also found differences in concentrations in amyloid positive participants. **Conclusions:** Due to associations of differences in plasma Aβ between amyloid positive and negative participants, our findings support the hypothesis that blood Aβ interacts with and may be at least partially derived from the CNS. The results also suggest that blood-derived Aβ may be useful as a screening test for CNS Aβ amyloidosis.

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In Vivo spreading Pathways of Tau and Amyloid Accumulation and Its Genetic Underpinnings

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Background: The spreading phenomenon of abnormal Tau and amyloid-b (Ab) proteins along neuronal circuits is critical to understand the foundations of Alzheimer's disease pathology. In this study, we aim to identify the in vivo spreading pathways of Tau and Ab deposits, as well as their genetic vulnerabilities, in a longitudinal sample of elderly participants in the Harvard Aging Brain Study. **Methods**: Eighty-eight subjects (age: 76.2 (6.2), M/F: 39/49), divided in two independent samples, were included in the study: 1) a cross-sectional sample of sixty-nine subjects; and 2) a 1-2 year follow-up longitudinal sample of nineteen subjects. Using Flortaucipir and PiB imaging, we developed a novel graph theory method to predict at cross-sectional level and confirm at longitudinal level the cerebral spreading pathways of Tau and Aβ accumulation. Then, we used the genetic transcriptome Allen Brain Atlas to evaluate which protein-encoding genes confer vulnerability for Tau and Ab neural propagation. Thus, we compared the regional phenotype of our cortical spreading pathways with regional gene expression levels in the human brain. **Results**: We found distinctive propagation pathways for Tau and Aβ accumulation, with high spatial correlations between cross-sectionally predicted and longitudinally observed network changes (all r>0.6). Particularly, medial/inferior temporal lobe areas project pathways of Tau-spreading toward anterior pole, lateral and posteriomedial temporal cortex, and orbitofrontal cortex, while posterior cingulate cortex spreads Aβ toward surrounding areas and lateral parietal lobe. Regional gene expression profiles of 133 genes were significantly associated with the Tau-spreading pathway, including MAPT gene. We also found 178 genes, including the CLU gene, significantly associated with the Ab pathway. Gene Ontology enrichment analysis characterized the Tau-spreading genetic profile as "axon-related" and the Ab-spreading genetic profile as "dendrite-related". In a genetic interactome analysis across Tau- and Ab-spreading genetic profiles, APOE arose as the most central gene linking Tau- and Ab-spreading pathways. **Conclusions**: We describe for the first time the in vivo spreading pathways of Tau and Aβ using a longitudinal brain network approach. Moreover, analysis of microarray-based gene expression data revealed distinct genetic profiles that may confer vulnerability for Tau- and Aβ-spreading circuits in the human brain.

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