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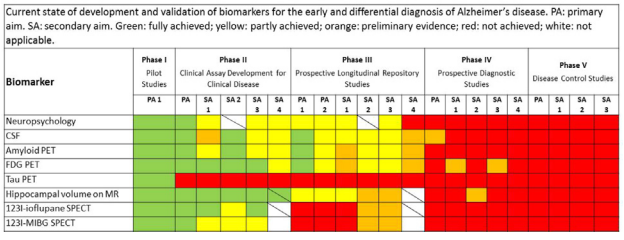
ALZHEIMER'S IMAGING CONSORTIUM (AIC)
IC-P
AMYLOID IMAGING

IC-P-001 18F-FLORBETABEN SUVR CUTOFF QUANTIFICATION ACROSS REFERENCE REGIONS AND STANDARDS OF TRUTH AND COMPARISON TO VISUAL ASSESSMENT

Susan De Santi[1], Ana M. Catafau[2], John P. Seibyl[3], Santiago Bullich[2], *[1]Piramal Pharma Inc., Boston, MA, USA; [2]Piramal Imaging GmbH, Berlin, Germany; [3]Molecular Neuroimaging, LLC, New Haven, CT, USA.*
Contact e-mail: Susan.De-santi@piramal.com

Background: The aims of this study were 1) to generate 18F-Florbetaben (FBB) SUVR cutoff values for different reference regions (RRs) using visual assessment (VA) as standard of truth (SoT); 2) to validate them across different clinical populations and SoTs and 3) to compare VA and SUVR cutoffs. **Methods:** For aim 1, SUVR cutoff was generated using FBB scans from a sample of 143 subjects (69.5±7.5 yrs; n=75 Alzheimer's disease (AD), n=68 healthy volunteers (HVs)) who were assessed by 3 blinded independent readers SUVR was calculated for different RRs: cerebellar gray matter (GCER), whole cerebellum (WCER), pons (PONS), and subcortical white matter (SWM). A SUVR cutoff value for each RR was generated using Receiver Operating Characteristic analysis, VA as the SoT, and highest accuracy as the selection criteria. For aim 2, SUVR cutoffs were validated in two different samples: Sample a) n=78 end-of life subjects (80.1±10.4 yrs) using VA from 5 readers and histopathological confirmation of the presence of neuritic beta-amyloid plaques as SoT and Sample b) n=233 subjects (72.6±7.3 yrs; n=118 HVs, n=115 AD) using VA from 8 readers and clinical diagnosis as SoT. For aim 3, FBB scans were visually assessed by 8 blinded readers. The number of correctly or incorrectly classified scans according to pathology results using VA and SUVR cutoffs for each RR was compared. **Results:** Aim 1: Composite SUVR cutoffs were 1.43 (GCER); 0.96 (WCER); 0.78 (PONS); 0.71 (SWM). Aim2: Accuracy values were high and consistent across SUVR cutoffs and VA methods and SoTs (range 83-94% for histopathology, 80-87% for clinical diagnosis and 86-97% for VA). Aim 3: A range of 63-71 cases were correctly classified by both SUVR cutoff (across RRs) and VA, while 1-3 cases (across RRs) were incorrectly classified by both SUVR cutoff and VA. SUVR cutoff method misclassified more cases (range:3-10 cases) than VA (range:1-3 cases) for any RR. **Conclusions:** 18F-FBB SUVR cutoff quantification is very robust. SUVR cutoff performance was high for all RRs, independent of the SoTs, and consistent with VA. The lack of differences across RR supports using the cerebellum as the most biologically appropriate one for 18F-FBB SUVR.

IC-P-002 ROADMAP TO THE BIOMARKER-BASED DIAGNOSIS OF ALZHEIMER'S DISEASE

Marina Boccardi[1,2], Yutaka Yasui[3,4], Chiara Cerami[5,6], Konstantinos Chiotis[7], Valentina Garibotto[8], Niklas Mattsson[9,10,11], Ida Sonni[12,13], Mara ten Kate[14], Corinna Porteri[15], Clifford R. Jack, Jr.,[16], Bengt Winblad[17], Giovanni B. Frisoni[18,19], Geneva Task Force for the Roadmap of Alzheimer's Biomarkers, *[1]IRCCS S Giovanni di Dio Fatebenefratelli, Brescia, Italy; [2]LANVIE - Laboratory of Neuroimaging of Aging, University of Geneva, Geneva, Switzerland; [3]School of Public Health, University of Alberta, Edmonton, AB, Canada; [4]St. Jude Children's Research Hospital, Memphis, TN, USA; [5]San Raffaele Turro Hospital, Milano, Università Vita-Salute San Raffaele, Milano, Italy; [6]Division of Neuroscience, San Raffaele, Scientific Institute, Milano, Italy; [7]Karolinska Institutet, Stockholm, Sweden; [8]Hôpitaux Universitaires de Genève, Geneva, Switzerland; [9]Clinical Memory Research Unit, Lund University, Lund, Sweden; [10]Memory Clinic, Skåne University Hospital, Lund University, Lund, Sweden; [11]Skåne University Hospital, Department of Neurology, Lund, Sweden; [12]Stanford University, Division of Nuclear Medicine and Molecular Imaging, Stanford, CA, USA; [13]Karolinska Institutet, Center for Psychiatry Research, Stockholm, Sweden; [14]Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands; [15]Bioethics Unit, IRCCS Centro San Giovanni di Dio, Brescia, Italy; [16]Mayo Clinic, Rochester, MN, USA; [17]Karolinska Institutet, Center for Alzheimer Research, Div. of Neurogeriatrics, Huddinge, Sweden; [18]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; [19]Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland.*
Contact e-mail: mboccardifbf@gmail.com

Background: The diagnosis of Alzheimer's disease (AD) is shifting from a clinical to a clinicalpathological paradigm. Biomarkers of Alzheimer's pathology (hippocampal atrophy on MR, cortical hypometabolismon FDGPET, decreased Abeta42 and increased tau and phosphotau in CSF, and increased amyloid and Tau ligands uptake on PET) are at different stages of development. The lack of coordinated development at the European and global level is delaying authorization by regulatory agencies, reimbursement by payers, implementation in the clinic, and ultimately the development of effective treatments. Objective: Outlining the actions required to accelerate this course. **Methods:** A group of European AD biomarker and international cancer biomarker experts adapted a 5phase framework for biomarker development used in oncology to AD biomarkers. The 5 sequential phases include: 1) pilot studies, 2) clinical assay development for clinical disease, 3) prospective longitudinal repository studies, 4) prospective diagnostic studies, and 5) disease control studies. Current maturity of biomarkers according to this framework was assessed from available literature on: neuropsychology; amyloidPET; TauPET; CSF Abeta42, tau and phosphotau; FDGPET; hippocampal atrophy, 123IIoflupane and 123IMIBG. **Results:** Literature evidence shows that all biomarkers validation studies fulfil Phase 1. The aims of phases 2 and 3 are addressed inconsistently and studies do not systematically follow the sequential order of the phases. Only preliminary evidence is available for some Phase 4 aims for amyloidPET, CSF biomarkers, hippocampal atrophy, and FDG PET. Phase 5 aims have never been addressed. Compared to other biomarkers, FDGPET and Amyloid imaging are at a relatively advanced stage of validation, while 123IIoflupane and 123IMIBG SPECT validity studies are relatively less advanced, TauPET being at a very initial stage of validation (Figure). **Conclusions:** This evidence highlights research priorities and identifies a roadmap of actions, aimed to accelerate AD biomarker implementation in the clinic. The intended users of the roadmap are funding agencies of healthcare research, scientists and scientific societies, and policy makers.