Supplementary Table 7. Index test and numbers of converters to Alzheimer’s disease dementia

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| **Study/**  **Study design** | **Threshold**  **(pre-specified**  **Yes/No)** | **Image scaling** | **Discriminating brain area** | **Image analysis** | **Time between 18F-FDG injection and PET acquisition (min)** | **18F-FDG dose** | **Number of 18F-FDG positive**  **(%)** | **Number of converters (%)** | **Duration of follow-up**  **Mean, Median, Range: months (m)/ years (y) / Maximum (m)/(y)** |
| **Anchisi 2005**  **(Italy)** | rCGMglc of temporoparietal and posterior cingulate of 1.138  (No) | Regional sensorimotor  18F-FDG uptake ratio (p.1730) | Bilateral parietal and posterior cingulate cortex | SPM99 | Not reported | Not  reported | 19/48  (40)  (calculated in RevMan5) | 14/48  (29) | Median  12 m  Range  12-27 m |
| **Arbizu 2013\*** | AD conversion score=0.28  (No) | Images were spatially normalized  to the pons region  (and spatially smoothed with a 3-D gaussian kernel with an  8-mm FWHM. | Bilateral parietal and temporal cortex, and posterior cingulate | SPM8 | 40 | 5.3 MBq/kg | 65/121 (54) | 36/121 (30) | Maximum  2 y |
| **Arnaiz 2001** | rCGMglc of left temporoparietal region 13 mm above the basal ganglia  (Model I)  (No) | Sensorimotor  area of the cortex 26mm above the level of the basal ganglia  (p. 852) | Temporo-parietal cortex | SPSS  (Herholz 1999) | 60 | Not  reported | 8/20  (40)  (calculated in RevMan5) | 9/20  (45) | On average  36.5 m |
| **Berent 1999**  **(USA)** | rCGMglc of  diagnostic index based on Z-scores of the parietal cortex  (No) | Thalamus  (p. 11) | Frontal, temporal, parietal and occipital regions normalized to the thalamus | 3-D-SSP | Not reported | 370 MBq | 10/20  (50) | 10/20  (50) | Maximum  3 y |
| **Bruck 2013** | 1.16 for 18F-FDG retention in the lateral frontal cortex  (No) | Images were spatially normalized  to the pons region or the cerebellar cortex | Lateral frontal (LFC) and temporal (LTC)cortex medial frontal and temporal cortex, parietal and occipital cortex, anterior cingulate, posterior cingulate/precuneus, caudate and putamen | ROI | 55 | 248 ±47.5 MBq | 13/22  (59) | 13/22  (59) | Maximum  2 y |
| **Chetelat 2003**  **(France)** | rCGMglc at Z-score of >3.09  Thresholding was set at 80% of whole brain mean of control subjects  (No) | FDG uptake normalized by and adjusted to the subject’s global uptake (p. 1375) | Right temporo-parietal and posterior cingulate | SPM99 | Not reported | Not  reported | 7/17  (41)  right temporo-parietal region  8 (47.0) posterior cingulate | 7/17  (41) | Maximum  18 m |
| **Choo 2013** | Parietal glucose metabolic rate =1.505  (No) | Images were spatially normalized  to the pons region | Frontal, temporal, parietal, posterior cingulate cortex and caudate | SPM | Not reported | Not  reported | 30/77  (39) | 26/77  (34) | Mean  44.0±35.4 m  Range  1.6-162 m |
| **Clerici 2009**  **(Italy)** | rCGMglc  lower that the control group corresponding to a *P* value <0.01 level)  (Yes) | Global counts were normalized by proportional scaling to remove confounding effects due to global changes  (Del Sole 2008) | Posterior gyrus cingulate and bilateral inferior frontal cortex | SPM(t) | 45 | 185-370 MBq | 23/26  (88.5) | 13/26  (50) | Maximum  18 m for aMCI  Maximum:  37 m for snaMCI |
| **Drzezga 2005**  **(Germany)** | rCGMglc at  Z-score of >1.64 (1 tail) corresponding to a *P* value of 0.05 (1 tail)  (Yes) | Not  reported | Orbitofrontal, prefrontal, premotor, central, parietal superior and inferior, occipital, temporal anterior, temporal posterior and posterior cingulate | 3-D-SSP | 30 | 370 MBq | 13/30  (43) | 12/30  (40) | Mean  16±2 m |
| **Dukart 2016\*** | No single threshold value used; the decision was made by the classifier based on the pattern seen in a set of AD relevant regions  (No) | Not reported | Not reported | SPM8 | Not reported | Not reported | 48/164  (29) | 29/164  (18) | Mean  33 m  Range:  7.3-61.4 m |
| **Fellgiebel 2007**  **(Germany)** | rCGMglc at  significantly decreased Z-score >2 in more than 50 adjacent pixels  (Yes) | Sensorimotor  area of the cortex (transaxial images parallel to the intercomissural line)  (Fellgiebel  2004) | Parietal mesial or posterior cingulate and temporal regions | SPSS  (Fellgiebel 2004) | 30  (Fellgiebel 2004) | 180 MBq (Fellgiebel 2004) | 7/16  (44) | 4/16  (25) | Mean  19.6±9.0 m |
| **Galluzzi 2010**  **(Italy)** | rCGMglc of  t sum > 11.090 (email from the author)  (Herholz 2002)  (Yes) | Cerebellum | Temporo-parietal, hippocampus and posterior cingulate | SPSS | Not reported | Not  reported | 28/38  (74) | 14/38  (37) | Mean  20.6.6±9.7 m |
| **Gommar 2014\*** | Not reported | Cerebrum | Not reported | SPM | Not reported | Not  reported | 59/162  (36) | 74/162  (46) | Maximum  4 y  Mean  33.3 m |
| **Grimmer 2016** | rCGMglc of  t sum =11.089  (Yes) | Not reported | Not reported | Neurostat/  3DD-SSP | Not described; standardized protocols followed | Not described; standardized protocols followed | 10/28  (36) | 9/28  (32) | Mean  31.2±7.8 m |
| **Herholz 2011\*** | rCGMglc of  t sum > 11.090  (Herholz 2002)  (Yes) | Global cortex | Temporal and parietal lobes | PALZ (PMOD software) | 30-60 | Not  reported | 38/94  (40) | 30/94  (32) | Maximum  2 y |
| **Hatashita 2013** | SUVR ≤0.99  (Yes) | A standardized uptake value (SUV) of the same region was obtained and subsequently normalized to the cerebellar cortex as reference | Not reported | SUVR images | 45 | 249.9±28.8 MBq | 57/68  (84) | 30/68  (44) | Mean  19.2±7.1 m |
| **Iaccarino 2015** | Voxel-wise SPM procedure  (presence or absence of AD-like or other dementia-like FDG patterns)  (Yes) | Not reported | Not reported | SPM-t maps, obtained through an optimized single-subject **SPM** analysis were evaluated by four neuroimaging experts (Cohen’s k: 0.89) | 45-60 | 214±45  MBq | 11/30  (37) | 14/30  (47) | Median  26.5 m  Inter-quartile range: 30 m |
| **Ito 2015** | 3D-SSP z-score map was constructed based on 50 normal subjects  (Yes) | Not reported | Not reported | Neurostat/  3D-SSP | 40-60 | 254±107 MBq | 43/88  (49) | 41/88  (47) | Maximum  3 y |
| **Landau 2010\*** | rCGMglc of 1.21  (No) | Cerebellar vermis and pons | ROI interest were study  independently frequently associated with decline in AD and MCI. No further details. | SPM5 | 30-60 | Not  reported | 51/85  (60) | 28/85  (33) | Mean  1.9±0.4 y  On average:  2 y |
| **Lange 2016\*** | t-sum=18774 (1199), determined by the maximum Youden index  (No) | Brain parenchyma | Five reference points located in precuneus, left/right parietotemporal and left/right lateral temporal cortex | t-sum | 30-60 | Not reported | 100/241 (42) | 60/241 (25) | Maximum  3 y |
| **Mosconi 2004**  **(Italy)** | rCMRglc significantly reduced in certain cerebral areas with emphasis on the inferior parietal lobule (IPL).  (No) | Global cortex | Precuneus, anterior and posterior cingulate, inferior parietal lobe, superior, middle and inferior frontal gyrus, on both hemispheres | SPM99 | 42 ± 19 | 110-370 MBq | 4/37  (10.5) | 8/37  (21) | Mean  12±0.6 m |
| **Nobili 2008**  **(Italy)** | Threshold not reported  Principal component analysis on VOI  (No) | Global cortex | 25 VROI (volumetric region of interest) in each hemisphere | Computerized Brain Atlas (CBA;  Applied Medical Imaging©, Uppsala, Sweden) | 45 | 370 MBq | 11/22  (33) | 11 /22  (33) | Mean  21.1±10.9 m |
| **Ossenkoppele 2012**  **(Netherlands)** | Threshold not reported  Visual inspection and SUVr of ROIs  Computer aided visual read  (No) | Cerebellar grey matter | Frontal, parietal and latero-temporal and medial temporal lobes and posterior cingulate | SUVr and ROI images | 45-60 | 150±17 MBq | 4/12  (33) | 4/12  (33) | Mean  30 m  Range  2-4 years |
| **Ossenkoppele 2012a**  **(Netherlands)** | Threshold not reported  Visual inspection and SUVr of ROIs  Computer aided visual read & automated hypometabolism (No) | Cerebellar grey matter (p. 3) | Frontal, parietal, occipital, and latero-temporal and medial temporal lobes and posterior cingulate | Combined SUVr images and ‘t-sum’  PMOD Alzheimer discrimination tool (PALZ) | 45-60 | 185 MBq | 5/12  (42) | 6/12  (50) | Maximum  2 years |
| **Pagani 2017** | Optimized threshold: a cut-off value was chosen as the minimum the distance from the upper left corner of the ROC curve (where specificity = sensitivity = 1) (No) | Images were reconstructed using an ordered subsets expectation maximization algorithm, with 16  subsets and six iterations, and a reconstructed voxel size of  1.33 × 1.33 × 2.00 mm. | FDG uptake values were calculated in 45 anatomical VOIs in each hemisphere and normalized in each subject to the average intensity of the cerebellar VOIs on the basis that the cerebellum is poorly affected by the AD pathological process | Meta-VOI metric | 15 | Not reported | 85/122  (70) | 95/122  (78) | Maximum  5 years |
| **Pardo 2010**  **(USA)** | Computer aided visual read  Visual inspection  (Only SVM analysis used thresholds)  (No) | PET scans were adjusted to a whole-brain mean activity and stereotactically normalized by using Neurostat (p. 328) | Frontal, parietal, occipital, and latero-temporal and medial temporal lobes and posterior cingulate | SVM | Not reported | 5 mCi/70 kg | Reader 1:  6/18  (32)  Reader 2:  10/18  (53) | 8/18  (44)  9/18  (47) | Maximum  3 years |
| **Perani 2014** | Optimized threshold: set up at p = 0.05, corrected for multiple comparisons with the family-wise error (FWE) option at the voxel level, and contained more than 100 voxels  (Yes) | PET scans were adjusted to a whole-brain activity | Brain lobes, i.e. frontal, temporal, parietal, occipital | sc-SPM | 45 | 18F-FDG PET acquisitions were performed according to the guidelines of the European Association of Nuclear Medicine (EANM). No further details | 11/23  (48) | 5/23  (22) | Mean  27.6±4.1 m |
| **Perani 2016** | Threshold from Perani 2014 used  (Yes) | As above in Perani 2014 | As above in Perani 2014 | sc-SPM | 45 | As above in Perani 2014 | 9/28  (32) | 8/28  (29) | Mean  27.5±10.4 m |
| **Prestia 2013\*** | PALZ  t-sum=13 481 for ADNI;  t-sum=13,481 for TOMC  HCI  1.055 for both samples  Meta ROI average w=2.60 for both samples | Images were reconstructed using the FORE-Iterative  algorithm (48 subsets, five iterations) with an xy and z filter (cut off of 4 mm), yielding a 128x128 matrix with a pixel size of 1.95mm (Caroli 2011) | Not reported | t-sum/HCI/  meta ROI average | Not reported | Not  reported | ADNI  PALZ  19/57 (33)  HCI  28/57 (49)  MetaROI  25/57 (44)  TOMC  PALZ  19/36 (52)  HCI  21/36 (58)  MetaROI  13/36 (36) | ADNI  24/57  (42)  TOMC  18/36  (50) | ADNI  Mean  36±12 m  Range  12-48 m  TOMC  Mean  26±12 m  Range  12-36 m |
| **Prestia 2015** | t-sum ˃11090  (Yes) | AD-related cortical hypometabolism | Brain regions typically affected in AD | t-sum/HCI | Not reported | Not reported | 29/73  (40) | 29/73  (40) | Mean  28±17 m |
| **Schmand**  **2012\*** | rCGM value of < 1.20  (Email from the author)  (Yes) | Not  reported | Right and left angular gyrus, bilateral posterior cingulate gyrus and left middle/inferior temporal gyrus | SPSS | Not reported | Not  reported | 18/89  (20) | 38/89  (43) | Mean  2.7±0.9 y  Range  0.5-4.6 y |
| **Shaffer 2013\*** | A weighted combination of loading parameters for about 5 different AD-specific metabolic patterns, and therefore is not a specific SUV value  (No) | Global cortex | Temporo parietal lobes and posterior cingulate region | SUVr | Not reported | Not  reported | 51/97  (52) | 43/97 (44) | Maximum  4 y |
| **Toussaint 2012\*** | Visual interpretation using SPM t-map | Global cortex | Medial frontal, anterior cingulate, right superior temporal and bilateral superior parietal regions. | sc-SPM | 30-60 | Not  reported | 44/80  (55) | 40/80  (50) | Maximum  2 y |
| **Trzepacz 2014\*** | Average rCMRglc. No further information.  Three laboratories analyzed the ADNI FDG-PET images using  different methods, resulting in several recommended summary statistics | Not reported | A number of ROI, i.e. frontal, parietal and temporal cortices; posterior cingulate | SUVr/ROI | 30 | 5 mCi ±10%) | 3/50  (6%) | 20/50  (40) | Maximum  2 y |
| **Young 2013\*** | Not reported | Not reported | A number of regions, i.e. temporal lobe, cingulate gyrus | Guassian classification | 30-60 | Not reported | 65/143  (45) | 47/143  (33) | Maximum  3 y |
| SVM classification | 48/143  (33.6) |

18F-FDG, Fluorine-18-2-fluoro-2-deoxy-D-glucose; PET, positron emission tomography; rCGMglc, Regional cerebral glucose metabolism; SPM, statistical parametric map; RevMan5, Review Manager software; AD, Alzheimer’s disease; 3-D, three-dimensional; SPSS, Statistical package for the Social Science; 3-D-SSP, 3-D stereotactic surface projection; PALZ, Probability of ALZheimer; SUVR, standardized uptake value ratio; ROI, region of interest; HCI, hypometabolic convergence index; TOMC, Transitional Outpatient Memory Clinic; SVM, support vector machine

\*ADNI study, Alzheimer’s Disease Neuroimaging Initiative cohort

Notes: Cerami 2015 not included in the Table; target condition was ‘conversion from MCI to All dementias’