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Christopher Rowe
Pierrick Bourgeat
Kathryn Ellis
Belinda M. Brown

Edith Cowan University, belinda.brown@ecu.edu.au

Lim Yen Ying

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Predicting Alzheimer Disease with \( \beta \)-Amyloid Imaging: Results from the Australian Imaging, Biomarkers, and Lifestyle Study of Ageing

Christopher C. Rowe, MD,1 Pierrick Bourgeat, PhD,2 Kathryn A. Ellis, PhD,3,4 Belinda Brown, BSc,5 Yen Ying Lim, PhD,3,4 Rachel Mulligan, PhD,1 Gareth Jones, BSc,1 Paul Maruff, PhD,3 Michael Woodward, MD,6 Roger Price, PhD,7 Peter Robins, MD,7 Henri Tochon-Danguy, PhD,1 Graeme O’Keefe, PhD,1 Kerryn E. Pike, PhD,1,8 Paul Yates, MD,1 Cassandra Szoike, MD,9 Olivier Salvado, PhD,2 S. Lance Macaulay, PhD,10 Timothy O’Meara, PhD,10 Richard Head, PhD,10 Lynne Cobic, PhD,10 Greg Savage, PhD,11 Ralph Martins, PhD,5 Colin L. Masters, MD, PhD,3 David Ames, MD,4,9 and Victor L. Villemagne, MD1,3

Objective: Biomarkers for Alzheimer disease (AD) can detect the disease pathology in asymptomatic subjects and individuals with mild cognitive impairment (MCI), but their cognitive prognosis remains uncertain. We aimed to determine the prognostic value of \( \beta \)-amyloid imaging, alone and in combination with memory performance, hippocampal atrophy, and apolipoprotein E \( \varepsilon 4 \) status in nondemented, older individuals.

Methods: A total of 183 healthy individuals (age \( 72.0 \pm 7.26 \) years) and 87 participants with MCI (age \( 73.7 \pm 8.27 \)) in the Australian Imaging, Biomarkers, and Lifestyle study of ageing were studied. Clinical reclassification was performed after 3 years, blind to biomarker findings. \( \beta \)-Amyloid imaging was considered positive if the \( 11 \)C-Pittsburgh compound B cortical to reference ratio was \( >1.5 \).

Results: Thirteen percent of healthy persons progressed (15 to MCI, 8 to dementia), and 59% of the MCI cohort progressed to probable AD. Multivariate analysis showed \( \beta \)-amyloid imaging as the single variable most strongly associated with progression. Of combinations, subtle memory impairment (Z score \( \leq 0.5 \) to \( \leq 1.5 \)) with a positive amyloid scan was most strongly associated with progression in healthy individuals (odds ratio [OR] = 16, 95% confidence interval [CI] = 3.7–68; positive predictive value [PPV] = 50%, 95% CI = 19–81; negative predictive value [NPV] = 94%, 95% CI = 88–98). Almost all amnestic MCI subjects (Z score \( \leq 1.5 \)) with a positive amyloid scan developed AD (OR = \( \infty \); PPV = 86%, 95% CI = 72–95; NPV = 100%, 95% CI = 80–100). Hippocampal atrophy and \( \varepsilon 4 \) status did not add further predictive value.

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Address correspondence to Dr Rowe, Department of Nuclear Medicine and Centre for PET, Austin Health, 145 Studley Road, Heidelberg, Victoria 3084, Australia. E-mail: christopher.rowe@austin.org.au

From the 1Austin Health, Department of Nuclear Medicine and Centre for Positron Emission Tomography, Heidelberg, Victoria; 2Commonwealth Science and Industrial Research Organisation Preventative Health National Research Flagship, Australian e-Health Research Centre—BioMedIA, Herston, Queensland; 3Florey Institute for Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria; 4Department of Psychiatry, University of Melbourne, Melbourne, Victoria; 5Centre of Excellence for Alzheimer’s Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Western Australia, Australia; 6Austin Health, Aged Care Services, Heidelberg, Victoria; 7Western Australia Positron Emission Tomography and Cyclotron Service, Sir Charles Gardiner Hospital, Perth, Western Australia, Australia; 8School of Psychological Science, La Trobe University, Bundoora, Victoria; 9National Ageing Research Institute, Parkville, Victoria; 10Commonwealth Science and Industrial Research Organisation Preventative Health Flagship, Parkville, Victoria; and 11Department of Psychology and Australian Research Council Centre of Excellence in Cognition and its Disorders, Macquarie University, Sydney, New South Wales, Australia.

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earlier and more accurate diagnosis of Alzheimer disease (AD) will aid the development of early intervention therapies and may assist clinical and social management of the disease. The necessity for dementia in the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and Diagnostic and Statistical Manual of Mental Disorders 3rd edition revised diagnostic criteria for probable AD confine diagnosis to a late stage of the illness after many years of symptoms and may reduce the likelihood of a useful outcome from therapeutic intervention. Even before dementia, 60% loss of entorhinal neurons has been documented in those in the mild cognitive impairment (MCI) phase of the illness. Imaging data now show that the accumulation of β-amyloid (Aβ) plaques, a pathological hallmark of AD, occurs over several decades before dementia, suggesting a wide time window for therapeutic intervention. Consequently, recently published research criteria by the International Work Group and the National Institute of Aging and Alzheimer's Association (NIA/AA) work group propose the diagnosis of AD prior to dementia through the use of biomarkers for the disease process in combination with episodic memory (EM) assessment. These biomarkers include Aβ imaging with positron emission tomography (PET). Prospective data are needed to validate this new approach to early diagnosis of AD and to inform clinicians on the appropriate clinical use of Aβ imaging, relative to or in combination with other AD biomarkers, and to ensure their appropriate incorporation into clinical trials.

The Australian Imaging, Biomarkers, and Lifestyle study of ageing (AIBL) commenced in 2006 and was designed to improve the understanding of the pathogenesis of AD by intensive and longitudinal study of a large cohort of older persons. AIBL now has prospective, longitudinal data to test the validity of the criteria for preclinical and prodromal AD. To that end, clinical outcome at 3-year follow-up relative to baseline cognitive measurements and several AD biomarker findings are reported.

Subjects and Methods

Participants
Written informed consent was obtained from all participants. Approval for the study was obtained from the Austin Health, St Vincent’s Hospital Melbourne, and Edith Cowan University Human Research Ethics Committees. Healthy control (HC) subjects aged >60 years were recruited by advertisement. Patients with MCI were recruited from dementia specialists in both public and private clinics. The baseline characteristics, methodology, and baseline findings from the AIBL imaging cohort have been published previously. To strengthen the present analysis, data obtained from 72 individuals (32 HC, 40 MCI) with 3 years of follow-up recruited prior to commencement of AIBL at the AIBL imaging core laboratory (Austin Health, Melbourne) with the same recruitment criteria and methods as AIBL have been included. The majority of these individuals subsequently enrolled into AIBL at their first 18-month review, but the very first assessment of each participant whether pre-AIBL or AIBL was used as the baseline for this report to avoid duplication of data and bias of the cohort toward stable clinical status. MCI subjects enrolled pre-AIBL were younger (71.3 ± 8.9 years vs 75.3 ± 7.1, p = 0.012) but had the same rate of progression to AD (63% vs 54%, p = 0.66). There were no other demographic differences between the pre-AIBL and direct entry AIBL MCI or HC subjects. In total 193 HC and 93 MCI participants entered the imaging cohorts. After 3 years, 10 HC subjects were lost to follow-up (2 died, 1 developed terminal cancer, and 7 withdrew) and 6 of the MCI subjects were lost to follow-up (5 died and 1 withdrew after a severe stroke).

After each visit (at 0, 18, and 36 months), participants were classified as HC, MCI, AD, or other dementia by consensus panel review of neuropsychological test scores and functional reports blind to biomarker findings. Diagnosis of AD was made as per NINCDS-ADRDA criteria for probable AD. Diagnosis of MCI was made as per Petersen and Winblad criteria. All HC participants performed within the published normal range for their age group on neuropsychological tests. Sixteen MCI and 5 HC subjects did not attend study centers for final follow-up. In these participants, an informant telephone interview was performed by a neurologist.

Neuropsychological Evaluation
All participants underwent extensive neuropsychological testing as described previously. However, in this report, only the California Verbal Learning Test-II long delayed free recall (CVLT-II LDFR) Z score derived from published, age-matched normal values was used to define EM performance at the baseline assessment so that findings could be readily applied to clinical practice.

Magnetic Resonance Imaging
All subjects underwent 3-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE), T2 fast spin echo and fluid-attenuated inversion recovery (FLAIR) sequences on 1.5T or 3T scanners. Subjects with history of stroke or a finding of a
cortical stroke based on interpretation of the T1 and FLAIR images by a neuroradiologist were excluded.

**PET**
As previously described, a 30-minute acquisition scan was performed with Allegro (Philips Medical Systems, Cleveland, OH) PET cameras at Austin Health for the Melbourne participants and the Sir Charles Gardiner Hospital for the Perth participants, starting 40 minutes after injection of ~370MBq $^{11}$C-Pittsburgh compound B (PiB).

**Image Analysis**
A preset in-house template of cortical regions of interest (ROIs) was applied to the PiB scan via placement on the subject's coregistered magnetic resonance imaging (MRI) by an operator (V.L.V.) who was blind to the subject's clinical status as previously described. Coregistration of PiB to MRI was performed with SPM5.15

Aβ burden was expressed as the average of the mean of frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate ROI activity per voxel divided by the cerebellar gray matter voxel activity and termed the standardized uptake value ratio (SUVR).

Hippocampal volume (HV) was calculated from T1 MPRAGE images after tissue segmentation using an implementation of the expectation maximization segmentation algorithm. The modified algorithm applied 9 MRI atlases with their associated tissue priors spatially normalized to each participant to provide 9 segmentation maps. A voting scheme then provided consensus for each voxel. As previously described, a hippocampal template was manually delineated on the Montreal Neurologic Institute single-subject template and then spatially normalized to each individual's study for hippocampus measurement. MRI data were normalized by dividing the HV by the total intracranial volume consisting of the sum of the cerebrospinal fluid (CSF), gray matter, and white matter volumes. The full pipeline is available as a plug-in of the open-source software MILXView (http://research.ict.csiro.au/software/milxview).

**Determination of Cutoff Values**
A negatively skewed and bimodal distribution of PiB SUVR was observed in HC subjects, and could not be normalized with data transformations. As reported previously, baseline PiB SUVR was classified as negative (PiB$, SUVR < 1.5$) or positive (PiB$^+$, SUVR $\geq 1.5$) based on the result of a hierarchical cluster analysis performed on all HC participants at Austin Health. This definition of PiB$^+$ (SUVR $\geq 1.5$) was used for the primary analyses in this report. However, 2-graph receiver operator curve (ROC) analysis$^{19}$ of the AIBL AD and HC cohorts gave an SUVR of 1.9 as the optimal cutoff for distinction of AD from age-matched HC subjects. This higher SUVR cutoff was subsequently used to define high PiB$^+$ (ie, AD-like) and low PiB$^+$ (SUVR = 1.5–1.9) to investigate whether AD-like, highly positive PiB scans had greater predictive value than mildly positive scans.

Given the normal distributions of MRI volumetrics in the AIBL HC and AD groups, a 2-graph ROC approach was applied to establish the optimal cutoff for HV (4.0cm$^3$) between them. This cutoff was then applied to the HC and MCI subjects in this study to determine the predictive value of hippocampal atrophy (HA).

For the HC group, subjects were classified as having subtle EM impairment (EM$^-$) when the CVLT-II LDFR $Z$ score was $-0.5$ to $-1.5$ below the published age- and gender-adjusted normal mean. Amnestic MCI required a CVLT-II LDFR $Z$ score of $\leq -1.5$.

Apolipoprotein E genotype was classified as $e4^+$ when 1 or 2 $e4$ alleles were present.

**Statistical Evaluation**
Data are presented as mean ± standard deviation unless otherwise stated. Correction for age or years of education was not applied to contingency table data analysis. Chi-square analyses were conducted to determine the extent to which each individual biomarker increased the risk of progression to MCI or AD. Combination biomarker pairs (both biomarkers positive vs both negative with exclusion of participants who had only 1 of the pair positive) were also analyzed. Odds ratios (ORs) and their 95% confidence intervals (CIs), positive predictive value (PPV), and negative predictive value (NPV) were calculated to provide an estimation of the magnitude of associations. If the OR could not be calculated due to a 100% NPV, Cox proportional hazard ratio was derived for this pair of tests. Probability values resulting from all statistics were corrected for multiple comparisons using false discovery rates. To determine which baseline risk factor was the strongest predictor of progression to MCI or AD, PiB, HV, EM, apolipoprotein E $e4$ status, age, and years of education were considered simultaneously in a stepwise logistic regression analysis that used the Wald forward selection method.

**Results**

**Healthy Elderly Cohort**
Characteristics of the healthy cohort are provided in Table 1. Participants were generally well educated, with an average of 13.5 years of education, and only 12% had a CVLT-II LDFR $Z$ score below -0.5. Twenty-three (13%) HC subjects progressed to MCI or dementia over 3 years (15 to MCI, 7 to AD, and 1 to vascular dementia). Only PiB$^+$ and EM$^+$ were significantly associated with progression, with ORs of 4.8 and 4.2, respectively. The combination of PiB$^+$ with EM$^+$, or with HV$, increased the risk to approximately 50% (Table 2).

For HC progression to MCI or dementia, the PPV for PiB$^+$ increased from 17% in those mildly PiB$^+$ to 37% in those with a high PiB$^+$ (AD-like) scan (Fig), but this was not significant. There were no baseline differences in gender, age, years of education, $e4^+$ prevalence, HV, or memory score between low PiB$^+$ and high PiB$^+$.
For the 8 HC subjects who progressed to dementia, PiB+ and HV+ were predictive, with ORs of 8.2 and 9.5, respectively, but with low PPV (11% and 13%, respectively).

Multivariate logistic regression indicated that PiB+ was the strongest predictor of progression to MCI or dementia 3 years after baseline (OR = 4.81, 95% CI = 1.84–12.58, Wald chi-square[1] = 10.25, p = 0.001). Years of education also predicted progression to MCI or dementia 3 years after baseline, although the OR was significantly lower (OR = 0.82, 95% CI = 0.71–0.95, Wald chi-square[1] = 7.35, p = 0.007). Age, e4+, HV+, and EM+ by themselves did not improve the prediction of disease progression (all Wald chi-square < 1.75, all p > 0.187). Analysis limited only to the 8 who progressed to dementia showed that HV+ (OR = 8.10, 95% CI = 1.4–39.1, Wald chi-square[1] = 5.40, p = 0.020) predicted progression to dementia, but e4+ and EM+ did not.

**MCI Cohort**

Characteristics of the MCI cohort are provided in Table 1. Fifty-one (59%) progressed to a clinical diagnosis of probable AD and 3 (3.4%) to other dementias over 3 years. Of those progressing to AD, 5 had a negative baseline PiB scan and all were e4 negative. PiB+ (OR = 14.5), amnestic MCI (OR = 10.6), e4+ (OR = 5.4), and HV+ (OR = 3.8) were all significantly associated with progression to probable AD (Table 3).

For progression from MCI to probable AD, the PPV increased significantly from 44% in those with a mildly PiB+ scan to 81% in those with a high PiB+ scan (see Fig; p = 0.027). There were no baseline differences in gender, age, years of education, e4+ prevalence, or HV between the low PiB+ and high PiB+ MCI subjects, but CVLT Z scores were significantly lower in the high PiB+ group (−1.83 ± 0.9 vs −3.14 ± 0.9, p = 0.003).

Of the MCI subjects with both PiB+ and amnestic MCI, the PPV was 86% for progression to probable AD and the NPV was 100% (see Table 3). The hazard ratio was >105 (p < 0.001). PiB+ with HV+ also showed a very high rate of progression to probable AD (PPV = 83%, OR = 44). The combination of PiB+ with e4+ did not add to the predictive power of PiB+ alone. There were insufficient PiB+ subjects with amnestic MCI without reduced HV to determine whether the addition of the HV biomarker increased predictive power.

Multivariate logistic regression indicated that PiB+ was most strongly associated with progression to probable AD 3 years after baseline (OR = 12.71, 95% CI = 2.89–55.90, Wald chi-square[1] = 11.32, p < 0.001). Amnestic MCI also predicted progression to probable AD, although the OR for this was numerically lower (OR = 6.26, 95%CI = 1.78–22.30, Wald chi-square[1] = 8.01, p = 0.005). With these factors accounted for, age, years of education, e4+, and HV+ did not improve significantly the prediction of progression to probable AD (all Wald chi-square[1] < 2.55, all p > 0.110).

### TABLE 1. Characteristics of the Healthy and Mildly Cognitively Impaired Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HC, n = 183</th>
<th>MCI, n = 87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr (SD)</td>
<td>72.0 (7.26)</td>
<td>73.7 (8.27)</td>
</tr>
<tr>
<td>Female, No., [%]</td>
<td>95 [51.9]</td>
<td>43 [49.4]</td>
</tr>
<tr>
<td>Education, yr (SD)</td>
<td>13.52 (3.73)</td>
<td>12.56 (4.27)</td>
</tr>
<tr>
<td>APOE ε4 carrier, No., [%]</td>
<td>74 [40.4]</td>
<td>50 [57.5]</td>
</tr>
<tr>
<td>PiB positive, No., [%]</td>
<td>53 [29.0], 29 high&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60 [69.0], 50 high&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Memory impairment, No., [%]</td>
<td>22 [12.0]</td>
<td>53 [60.9]</td>
</tr>
<tr>
<td>Reduced hippocampal volume, No., [%]</td>
<td>46 [26.2]</td>
<td>48 [67.6]</td>
</tr>
<tr>
<td>Progressed to AD at 36 months, No., [%]</td>
<td>7 [3.8]</td>
<td>51 [58.6]</td>
</tr>
<tr>
<td>Progressed to dementia at 36 months, No., [%]</td>
<td>8 [4.1]</td>
<td>55 [63.2]</td>
</tr>
</tbody>
</table>

<sup>a</sup>High PiB positive is defined as standardized uptake value ratio > 1.9.<br>
<sup>b</sup>Defined by California Verbal Learning Test-II delayed free recall Z score as ≤ −0.5 for HC and ≤ −1.5 for MCI.<br>
<sup>c</sup>Magnetic resonance imaging assessments on 175 HC and 71 MCI subjects.
Discussion

A key finding of this study was that healthy individuals with a positive Aβ scan, who also have a subtle reduction in EM or HA, have a significant risk of progression to MCI or AD over 3 years, sufficient risk to warrant early intervention trials in such individuals. In this study the risk was 50%, but the confidence interval was wide, so more data are required to better define the magnitude of this risk. Multivariate analysis demonstrated that the presence of Aβ plaques detectable by PET was the main influence in these prediction pairs. This finding supports the staging of preclinical AD proposed by the NIA/AA workgroup, indicating that individuals who are biomarker positive for Aβ and also have subtle memory impairment or biomarker evidence of neurodegeneration are at a more advanced stage in the development of AD and at greater risk of disease manifestation than those with only a positive Aβ biomarker. This finding is consistent with what we and others have recently shown in regard to the relationship between Aβ accumulation and other features of AD. The accumulation of Aβ occurs over 2 to 3 decades and can be detected at low levels with PiB PET 15 to 20 years before the typical levels found in patients with the clinical diagnosis of probable AD are achieved. In contrast, these studies suggest that HA and EM impairment are not detectable in an individual until approximately 5 years before dementia.

There are few previous reports from longitudinal studies to validate the NIA/AA criteria for preclinical AD. The Mayo Clinic Study of Aging has reported that after 1 year, 43% of healthy elderly who had subtle memory impairment, a positive PiB scan, and reduced HV progressed to MCI or dementia. The Knight Alzheimer’s Disease Research Center at Washington...
The second key finding is that >80% of individuals meeting the criteria for prodromal AD, that is, clear objective EM impairment with a positive biomarker for AD, will develop dementia and meet clinical criteria for probable AD within 3 years if the AD biomarker is Ab imaging. In this study, although there was overlap of CIs on bivariate analysis, Ab imaging with PiB PET appeared to perform substantially better than MRI measures of HA in identifying individuals with MCI who would progress to Alzheimer dementia (OR = 14.5 vs 3.8). This was supported by the results of multivariate analysis that showed PiB PET to be the strongest predictor of progression to AD. Nevertheless, there was considerable gain in positive predictive power from the presence of both imaging biomarkers (OR = 44, PPV = 83%). However, even greater predictive accuracy was obtained by combining clear objective evidence of EM impairment (ie, amnestic MCI) with a positive PiB scan (PPV = 86%, NPV = 100%), consistent with past reports that EM is the cognitive domain most affected in early AD and has good predictive accuracy for AD in MCI cohorts.

The predictive value of Ab imaging for progression from MCI to AD has been reported previously. Pooling those studies that, like the present study, used neuropsychological criteria for MCI, reveals progression to AD occurred in 60% if PiB compared to 7% if PiB over an average of 2 years of follow-up. We observed a higher rate of progression to a clinical diagnosis of AD in the PiB MCI patients of 19% (5 of 27). Given the well-documented deficiencies in the clinical diagnosis of probable AD compared to postmortem neuropathological diagnosis, particularly in distinguishing AD from other forms of dementia, the observation that 9% (5 of 58) of the MCI cohort that progressed to probable AD were PiB is consistent with the reported rate of misdiagnosis. All 5 did not carry the apolipoprotein E allele that is present in the majority of patients with AD, further suggesting that these individuals have been incorrectly diagnosed.

**Limitations**

Potential limitations of this study relate to the composition of the healthy elderly cohort, that the diagnosis of AD was not confirmed by histopathology, that EM status relied on 1 test, and that other biomarkers for AD such as CSF Ab and tau and 18F-fluorodeoxyglucose PET were not available for comparison in AIBL. The healthy elderly cohort contained a higher proportion of apolipoprotein E allele carriers than found in general population surveys (see Table 1), thereby increasing the proportion likely to have a positive PiB scan and the risk for progression to AD. This could increase the predictive power of all the investigations in the HC cohort, particularly amyloid imaging. The HC participants were recruited by advertisement, not random selection from the community, were generally well educated, and performed better on memory tasks than expected from the published age- and gender-matched normal range. Therefore, it may only be appropriate to apply our definition of subtle memory impairment and its prognostic implication to similar volunteer cohorts or members of the general population who have at least 12 years of education.

EM was classified on the results from 1 test, the CVLT-II LDFR, and its published normal range, for reasons stated below. Other tests or a combination of EM measures could have different ability to predict clinical progression.

In a recent meta-analysis, the combination of CSF Ab and tau yielded an OR of 18 (95% CI = 10–32) for progression from MCI to dementia, similar
to the results for PiB PET in the present study. More recently, a study from Washington University reported that both PiB PET and CSF tau to Aβ1-42 ratio were strongly associated with progression from HC status to AD. As the AIBL study did not collect CSF at entry in this cohort, we were not able to compare our findings with CSF biomarkers.

**Applicability to Clinical Practice**

At the present time, preclinical detection of AD pathology is for research purposes and not recommended for clinical practice. Amyloid imaging has recently been recommended for detection of AD-related pathology in individuals with MCI in the appropriate clinical setting as part of a comprehensive assessment by a dementia specialist. Therefore, where possible, methods that can be applied in clinical practice were used in this analysis. Consequently, although the AIBL study employs an extensive battery of neuropsychological tests, this analysis only used a well-known and widely available word list recall task, the CVLT-II, and its published normal range, to classify EM performance. Likewise, a binary classification of the Aβ scans as positive or negative was used to be consistent with current clinical practice. The quantitative cutpoint for a positive Aβ PET scan of SUVR = 1.5 correlates well with the threshold for visual detection of Aβ. However, this cutpoint is well below the mean of the AD patients in AIBL (mean SUVR = 2.3). The risk for progression in both HC and MCI subjects was substantially higher in those with a high positive (AD-like) PiB scan than in those with a low positive scan (see Fig). This suggests that clinical practice should take into account levels of Aβ.

**Conclusions**

These prospective data from the AIBL study validate the proposed criteria for preclinical and prodromal AD. A positive amyloid scan when associated with amnestic...
MCI is a powerful predictor of clinical progression and may be used in clinical practice to provide earlier diagnosis of AD and more accurate prognosis than can be achieved by clinical assessment alone. Amyloid imaging with memory assessment also identifies healthy older persons at high risk for clinical progression, which may prove useful for early intervention trials in preclinical AD that require a defined cognitive endpoint within a 3-year timeframe.

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Several coauthors were employees of CSIRO and contributed to study design, data collection, and analysis. None of the other entities had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Authorship

Potential Conflicts of Interest

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