Evaluation of a Calibrated ^{18}F-FDG PET Score as a Biomarker for Progression in Alzheimer Disease and Mild Cognitive Impairment

Karl Herholz[1], Sarah Westwood[1], Cathleen Haense[1], and Graham Dunn[2]

[1]Wolfson Molecular Imaging Centre, School of Cancer and Enabling Sciences, University of Manchester, Manchester, United Kingdom; and [2]School of Community Based Medicine, University of Manchester, Manchester, United Kingdom

Increasingly, clinical trials are being planned in patients with mild cognitive impairment (MCI) to prevent or delay the onset of dementia in Alzheimer disease (AD) by disease-modifying intervention. Inclusion of imaging techniques as biomarkers for patient selection and assessment of outcome is expected to increase trial efficacy. PET using ^{18}F-FDG provides objective information about the impairment of synaptic function and could, with appropriate standardization, qualify as a biomarker. **Methods:** We evaluated a predefined quantitative measure (PET score) that is extracted automatically from ^{18}F-FDG PET scans using a sample of controls ($n = 44$), patients with MCI ($n = 94$), and patients with mild AD ($n = 40$) from the Alzheimer Disease Neuroimaging Initiative (ADNI). Subjects received 4 scans and clinical assessments over 2 y. **Results:** PET scores provide much higher test–retest reliability than standard neuropsychologic test scores (Alzheimer's Disease Assessment Scale–Cognitive [ADAS-cog] and Mini-Mental State Examination) and superior signal strength for measuring progression. At the same time, they are related linearly to ADAS-cog scores, thus providing a valid measure of cognitive impairment. In addition, PET scores at study entry in MCI patients significantly predict clinical progression to dementia with a higher accuracy than Mini-Mental State Examination and ADAS-cog. **Conclusion:** ^{18}F-FDG PET scores are a valid imaging biomarker to monitor the progression of MCI to AD. Their superior test–retest reliability and signal strength will allow the reduction in the number of subjects needed or shortening of study duration substantially.

Key Words: neurology; PET; ^{18}F-FDG; dementia; mild cognitive impairment

It is unlikely that drugs or other interventions would be able to reverse the symptoms of manifest dementia in Alzheimer disease (AD) because extensive and irreversible microstructural neuronal changes have already occurred at the time of clinical manifestation of dementia. Thus, there is an urgent need and interest to conduct clinical trials during the prodromal phase in patients with mild cognitive impairment (MCI), with the aim to prevent or at least delay the onset of dementia by disease-modifying intervention (1).

It is currently difficult to perform such trials because the implementation of clinical criteria for MCI and referral pathways that affect patient selection differ widely between centers, resulting in substantial patient sample heterogeneity in multicenter trials and poor comparability of patient samples between trials. Furthermore, most neuropsychologic tests used as standard outcome criteria have substantial measurement variation, and their sensitivity to changes that are typically occurring in MCI patients is limited. Using progression to dementia as the main outcome criterion usually has the disadvantage that it is not completely objective and only a minority of MCI patients will develop clinical dementia within 1–2 y (2). These factors limit the statistical power and thus increase the sample size and associated trial cost. These problems could potentially be overcome by the use of imaging biomarkers as primary outcome parameters with reduced variation. However, for qualification as outcome parameters, their close relationship with clinically relevant outcome has to be demonstrated (3). This should then result in smaller sample size or shorter trial duration without loss of study power.

PET with the widely available tracer ^{18}F-FDG measures local glucose metabolism as a proxy for neuronal activity at a resting state. Impaired activity in AD is evident as reduced ^{18}F-FDG uptake predominantly in temporoparietal association areas, including the precuneus and posterior cingulate (4). These changes become detectable in individual subjects as significant deviation from controls 1–2 y before onset of dementia and are closely related to cognitive impairment (5). Compared with MRI morphometry, which is most sensitive in detecting and monitoring hippocampal atrophy and closely related to performance in memory tasks (6), ^{18}F-FDG PET is more sensitive in detecting neuronal dysfunction in neocortical association areas. The function of these areas is primarily related to cognitive deficits in nonmemory domains such as language and orientation (7),

which are of particular interest at the stage of transition from a relatively pure memory deficit in MCI to a more extensive cognitive impairment that characterizes dementia. Thus, ^{18}F-FDG PET appears to be particularly well suited for monitoring of progression at that stage, and a preliminary study indicated a substantial increase of study power in clinical trials using regional ^{18}F-FDG uptake as an outcome parameter (8). This potential has recently also been demonstrated by analysis of data from the Alzheimer Disease Neuroimaging Initiative (ADNI), using standard region-based linear modeling (9), and use of a specifically tailored region of interest to maximize sensitivity and specificity (10).

In a previous multicenter study, Herholz et al. (11) developed a measure to quantify the severity of metabolic impairment in AD on ^{18}F-FDG PET scans in an objective manner using an automated procedure, now available commercially as a standard image processing software tool (module PALZ; PMOD Technologies). It has already been applied to cross-sectional ADNI data, demonstrating its robustness and comparability of results in independent large data samples from multiple centers (12). Recently, the large multicenter longitudinal study conducted by the ADNI has compiled a comprehensive sample of healthy controls and patients with MCI and mild AD, providing clinical and ^{18}F-FDG PET data at 4 subsequent times over 2 y. We are therefore now analyzing the properties of the predefined standardized automatic procedure for ^{18}F-FDG PET scans as a candidate biomarker with respect to its reproducibility in controls, correspondence with clinical parameters in patients, signal strength for monitoring progression, and power to predict future progression.

MATERIALS AND METHODS

Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-y public–private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biologic markers, and clinical and neuropsychologic assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness and the time and cost of clinical trials. The principal investigator of this initiative is Michael W. Weiner, VA Medical Center and University of California–San Francisco, and ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations. Subjects have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, aged 55–90 y, to participate in the research—approximately 200 cognitively healthy older individuals to be followed for 3 y, 400 people with MCI to be followed for 3 y, and 200 people with early AD to be followed for 2 y. Up-to-date information is provided at www.adni-info.org.

Data for analysis were downloaded from the ADNI Web site in July 2010, including ^{18}F-FDG PET scans and associated clinical and neuropsychologic data. Inclusion criteria for download were completeness of the following items: date of birth, current diagnosis (healthy, MCI, or AD), Mini-Mental State Examination (MMSE), clinical dementia rating, Alzheimer's Disease Assessment Scale–Cognitive (ADAS-cog), and date of PET scans. Participants were required to have had four ^{18}F-FDG PET scans at baseline, 6 mo, 12 mo, and 24 mo.

PET scans represented the brain activity 30–60 min after injection of ^{18}F-FDG; had been reconstructed using 3-dimensional backprojection, 3-dimensional ordered-subset expectation maximization, or Fourier rebinning/2-dimensional ordered-subset expectation maximization; were scaled to a common global average value; and were reoriented into a standard $160 \times 160 \times 96$ voxel image grid (voxel size, $1.5 \times 1.5 \times 1.5$ mm) along the anterior commissure-posterior commissure (AC-PC) plane and formatted as DICOM or ECAT files. From these scans, we calculated the AD t-sum, as described in previous publications (11,12), using the procedure implemented as module PALZ in the PMOD software package (version 3.2; PMOD Technologies). The AD t-sum indicates the severity of the metabolic decrease in those brain areas that are typically being affected by AD (multimodal association cortices mostly located in the temporal and parietal lobes), including an adjustment for age effects.

In the present study, the AD t-sum was converted into a PET score by reference to its upper normal limit, as determined previously (11), and log transformation to approach a normal distribution of values, according to the following equation:

$$PETscore = \log 2 \{(ADtsum/11,089) + 1\}.$$

Results were analyzed using the R software package (R Foundation for Statistical Computing), mainly with regression analysis (function, lm) and a mixed-model ANOVA (function, ezANOVA), as indicated in the text. Random effects and instrumental variable (IV) models were fitted using xtreg and ivregress commands in Stata software (version 11; StataCorp), respectively. Instrumental variable models were fitted by maximum likelihood in Mplus (version 5.21; Muthén & Muthén).

RESULTS

Findings in Diagnostic Groups (at Each Time Point)

The basic demographic data are listed in Table 1. Ages were comparable between groups, and MMSE scores indicate that most AD patients were still only mildly demented at study entry.

As to be expected, the number of patients diagnosed with AD increased over time, whereas there was a decrease of patients who were diagnosed with MCI. The number of controls increased slightly because there were more MCI patients reclassified as controls during follow-up than the reverse. There were no substantial changes of PET scores over time in controls and in subjects diagnosed as MCI at each time point (Table 2)—a result to be expected because subjects with substantial clinical progression moved to the AD group. In contrast, there was a steady increase of PET scores in AD patients, because those who already had AD at entry remained in this group while the disease progressed.

TABLE 1
Demographics

| Diagnosis | n | Sex | | Age (y) | Clinical dementia rating | MMSE | ADAS-cog |
		M	F				
Control	44	27	17	75.8 ± 4.8	0	29.1 ± 0.88	7.4 ± 3.1
MCI	94	66	28	75.0 ± 7.6	0.5	27.1 ± 1.59	10.6 ± 4.0
AD	40	21	19	75.8 ± 6.4	0.83 ± 0.24	23.4 ± 1.95	18.8 ± 5.9

Data are mean ± SD.

The frequency of abnormal PET findings was low (~10%–20%) in healthy controls, 40%–50% in MCI patients, and stably around 85% in AD patients. These proportions were similar at all time points.

When patient groups based on their diagnostic classification at entry without diagnostic reclassification were followed (Table 3), the PET score in AD patients increased by 6.3% at 6 mo, 9.0% at 12 mo, and 25.6% at 24 mo (repeated-measures ANOVA, $P < 0.0001$); the latter 2 times were significant using the Fisher least-significant-difference test. A similar increase, significant already at month 6, was observed in MCI patients by 6.3%, 14.9%, and 28.1% after 6, 12, and 24 mo, respectively, whereas controls remained essentially stable. The progression toward more severe cognitive impairment in MCI and AD patients was also reflected in a decrease of MMSE scores.

Prediction of Outcome After 24 Months

Then, subjects were assigned to groups defined by comparison of diagnoses at baseline and at the ultimate follow-up evaluation at 24 mo. Of the 44 controls, 42 remained in that category, and 2 progressed to MCI. Of the 94 patients entering the study as MCI, 7 reverted to control status, 57 remained MCI, and 30 progressed to AD. All patients with manifest AD at baseline remained in that category at follow-up.

PET scores were significantly different between these groups (ANOVA, $F_{5,173} = 20.479$, $P < 0.0001$). AD patients and subjects progressing to a more severe diagnostic category (controls to MCI and MCI to AD) had significantly higher scores than stable controls and MCI patients (Fig. 1). In contrast, ADAS-cog and MMSE at baseline were different between the main diagnostic groups but did not differ significantly between progressive and nonprogressive MCI.

Subjects who had a PET score at baseline above 1 had a significantly increased risk for progression. The sensitivity to predict progression was 0.57; specificity, 0.67; positive predictive value, 0.45; and negative predictive value, 0.77. The area under the receiver-operating characteristic curve

TABLE 2
PET Findings in Controls, MCI, and AD at Each Time Point

| Diagnosis | Month | | | |
	0	6	12	24
Control				
n	44	48	48	49
MMSE	29.1 ± 0.88	29.1 ± 0.78	29.2 ± 1.22	29.1 ± 1.01
ADAS-cog	7.4 ± 3.1	6.6 ± 3.1	6.1 ± 3.0	5.7 ± 3.2
PET score	0.64 ± 0.37	0.63 ± 0.37	0.67 ± 0.36	0.67 ± 0.36
% PET abnormal	11	17	21	16
MCI				
n	94	88	79	59
MMSE	27.1 ± 1.58	26.8 ± 2.52	26.9 ± 2.35	27.1 ± 2.56
ADAS-cog	10.6 ± 4.0	11.5 ± 4.6	11.7 ± 5.1	11.9 ± 5.1
PET score	1.01 ± 0.62	1.08 ± 0.67	1.13 ± 0.70	1.07 ± 0.65
% PET abnormal	40	47	49	44
AD				
n	40	42	51	70
MMSE	23.4 ± 1.95	22.8 ± 3.33	21.8 ± 3.92	21.3 ± 4.49
ADAS-cog	18.8 ± 5.91	19.5 ± 5.60	20.8 ± 8.33	22.2 ± 10.18
PET score	1.74 ± 0.79	1.85 ± 0.83	1.84 ± 0.81	2.05 ± 0.88
% PET abnormal	85	86	85	86

Data are mean ± SD.

TABLE 3
Changes (Difference from Baseline) Within Diagnostic Groups

Diagnosis at entry	Month		
	6	12	24
Controls			
MMSE	−0.068 ± 1.087	0.090 ± 1.326	−0.068 ± 1.265
ADAS-cog	−0.720 ± 3.224	−1.250 ± 3.384	−1.211 ± 2.950
PET score	−0.015 ± 0.010	0.022 ± 0.136	0.032 ± 0.166
MCI			
MMSE	−0.298 ± 2.184	−0.564 ± 2.227	−1.255 ± 3.054
ADAS-cog	0.791 ± 3.687	1.429 ± 4.254	2.199 ± 4.582
d (ADAS-cog)	0.215	0.336	0.480
PET score	0.065 ± 0.235	0.150 ± 0.264	0.286 ± 0.350
d (PET)	0.276	0.568	0.817
AD			
MMSE	−0.750 ± 3.053	−1.975 ± 3.570	−3.350 ± 3.997
ADAS-cog	1.009 ± 3.528	3.209 ± 5.050	7.835 ± 7.604
d (ADAS-cog)	0.286	0.635	1.030
PET score	0.109 ± 0.307	0.175 ± 0.308	0.456 ± 0.417
d (PET)	0.355	0.568	1.094

Data are mean ± SD and Cohen d as indicated.

(Fig. 2) was 0.75, compared with 0.68 for ADAS-cog and 0.66 for MMSE.

Reproducibility and Signal Strength of Measurement

PET scores in stable controls did not change significantly over time in repeated-measures ANOVA (Table 4). On the basis that these subjects are not expected to show any significant change when measured repeatedly, we used them to assess measurement reproducibility. Assuming that the SD for change over 6 mo nearly entirely reflects measurement variation, the figures translate into a coefficient-of-measurement variation of 16%. At months 12 and 24, variation goes up slightly, most likely reflecting the increasing effect of biologic variation as time passes even in controls. The estimate of reliability (intraclass correlation) is 0.922 (95% confidence interval, 0.886–0.958). The signal strength, defined analogous to Cohen d as the difference of mean values relative to measurement variation, for distinction between AD and controls was 10.9 (score difference, 1.11 divided through measurement SD 0.101).

In contrast to PET scores, ADAS-cog scores did show a mild but significant ($P = 0.04$) decline in these subjects, probably because of training effects (Table 5). The coefficient-of-measurement variation was 40%, considerably larger than for PET scores; it did not go up over time, probably indicating that measurement variation was still dominating over biologic variation even at 24 mo. The estimate of reliability (intraclass correlation) was 0.472 (95% confidence interval, 0.317–0.627). Allowing for temporal change (as a fixed effect in a mixed-effects model) increases this reliability by a relatively trivial amount (new estimate, 0.485; 95% confidence interval, 0.337–0.635). The signal strength for distinction between AD and controls (score difference, 11.3) was 3.9, less than half that of PET.

Changes in Progressive Versus Nonprogressive MCI

The increase of PET scores was more closely related to disease progression in MCI patients, as detected clinically by development of dementia during follow-up, than the increase of ADAS-cog scores (Table 6). This difference was most clearly seen at 12 mo, when the increase of PET scores was significantly higher in progressing than in nonprogressing patients, whereas the increase of ADAS-cog was not. In terms of signal strength (Cohen d), the change
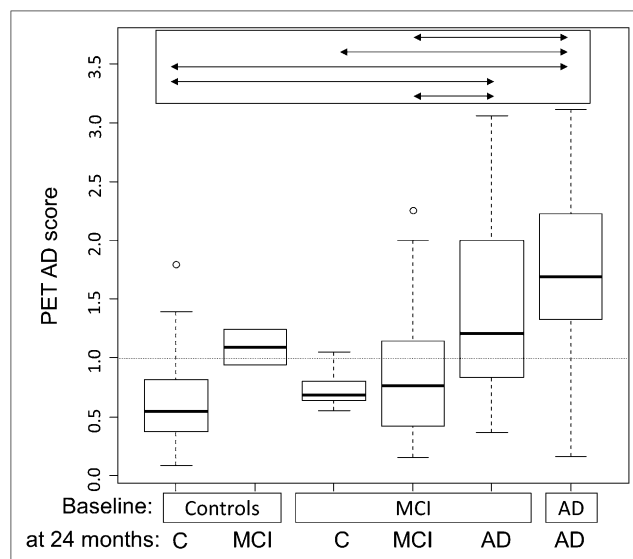
FIGURE 1. Box plot of baseline PET AD scores (interquartile and full range) for diagnostic groups. AD patients and MCI patients progressing to AD have significantly higher scores than stable subjects (arrows in top insert, $P < 0.05$ in Tukey multiple comparisons). C = control.
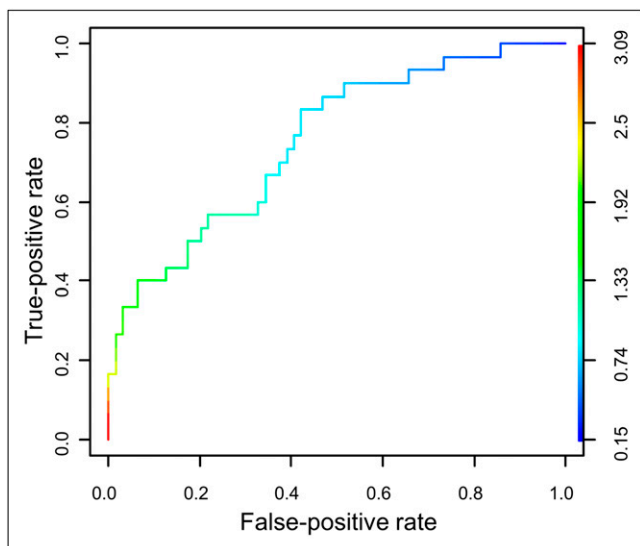
FIGURE 2. Receiver-operating-characteristic curve for prediction of progression of MCI to AD by PET score at entry.

of PET scores as outcome parameter over 12 mo provided nearly the same study power as the ADAS-cog scores over 24 mo.

Relative Calibration of PET Score Against ADAS-cog

There is a close and highly significant correlation between PET scores and ADAS-cog ($r = 0.63$, Fig. 3) and MMSE scores ($r = -0.63$) using all available data. Highly significant correlations also exist between the changes of ADAS-cog and PET scores over 24 mo ($r = 0.47$); they are close, especially in progressing MCI subjects ($r = 0.59$). Considering baseline data only, to avoid any distortions introduced by practice effects in ADAS-cog, the correlation between PET score and ADAS-cog is 0.55, with the corresponding regression coefficient (effect of PET on ADAS) estimated to be 4.52 using ordinary least squares (SE, 0.52). However, the latter estimate will be attenuated by measurement errors in the PET score. If we allow for measurement error in both variables, then the model is unidentified (in particular, we cannot estimate the required regression coefficient).

Both scores, ADAS-cog and PET, will yield a value of zero in the absence of any abnormality. Although absence of abnormality does not usually occur in actual measure-

TABLE 4
PET Scores in Stable Control Subjects

| Subject no. | Month | n | Mean | SD | Change relative to baseline | |
					Mean	SD
1	0	42	0.622	0.363		
2	6	42	0.610	0.384	−0.012	0.101
3	12	42	0.647	0.358	0.026	0.137
4	24	42	0.655	0.376	0.034	0.170

TABLE 5
ADAS-cog Scores in Stable Control Subjects

| Subject no. | Month | n | Mean | SD | Change relative to baseline | |
					Mean	SD
1	0	42	7.119	2.856		
2	6	42	6.563	3.117	−0.556	2.87
3	12	42	5.945	3.024	−1.174	3.376
4	24	42	5.739	2.951	−1.38	2.776

ments because even healthy controls will usually show some mild abnormalities, it is reasonable to assume a zero intercept in the linear model relating ADAS-cog to PET score. Then, the regression coefficient can be simply estimated by the ratio of the means of the 2 variables ($12.680/1.195 = 10.61$). Alternatively, IV regression (13) provides an estimate of the regression coefficient without the need for assuming a zero intercept. The resulting IV estimate was 10.58 (SE, 1.29) using the 2 binary dummy variables distinguishing the 3 diagnostic groups as instruments. Repeating the IV regression after replacing the initial diagnosis by baseline MMSE score as the instrument yielded a similar value (11.93; SE, 1.57). Finally, refitting the IV model using maximum likelihood, with an additional zero intercept constraint, yielded a similar estimated value of 10.70 but with a considerably smaller SE (0.43). In our discussion in the "Power Analysis" section, we will therefore assume the true difference in scale is a multiplicative factor of 10.6.

Power Analysis

We now turn to considering recalibrated PET scores by multiplying by a factor of 10.6. Thus, the PET score changes will have approximately the same scale of measurement as those for ADAS-cog. Using the whole sample (regardless of diagnosis), we obtain the changes from baseline to 12 mo and to 24 mo for the 2 measures as shown in Table 7.

As would be expected from the recalibration, the means of changes in PET score and ADAS-cog at each follow-up time are almost the same. A considerable increase in Cohen d for the PET scores, compared with ADAS-cog, is due to less variance in the PET data. At both follow-up times, the variance of the ADAS changes was about 3 times that of the PET score changes. For planning a randomized clinical trial using a simple t test to compare the outcomes of 2 randomized groups, the sample size (per group) required for a specified significance level and power is proportional to σ^2/δ^2, where σ^2 is the common variance of the outcome assessments and δ^2 is square of the true treatment effect to be detected. If (after appropriate calibration) the treatment effect (δ) is the same for the 2 competing outcome measures, and assuming that the common within-group variances will be similar to those described above (or, at least their ratio will be ~3), then the sample size required for

TABLE 6
Increase of Scores at 12 and 24 Months by Disease Progression in MCI Patients

Method	Progressive MCI	Nonprogressive MCI	P	Cohen d
12 mo				
PET	0.25 ± 0.31	0.10 ± 0.23	0.0087	0.55
ADAS-cog	2.3 ± 4.5	1.0 ± 4.1	NS	0.30
24 mo				
PET	0.45 ± 0.39	0.21 ± 0.31	0.0014	0.68
ADAS-cog	4.1 ± 5.1	1.3 ± 4.1	0.0058	0.60

NS = not statistically significant.
Data are mean difference ± SD, compared with baseline.

a trial using the ADAS-cog as the primary outcome will need to be about 3 times that needed if PET scores are used. Alternatively, when using PET scores, one could keep the sample size the same but shorten the follow-up times—the ratio σ^2/δ^2 (the square of the inverse of Cohen d) for the PET scores at 12 mo being close to ADAS cog at 24 mo and for PET scores at 6 mo being close to ADAS-cog scores at 12 mo.

DISCUSSION

Our analysis is based entirely on a predefined, commercially available, and user-independent procedure for ^{18}F-FDG PET scans. Our analysis is in contrast to that of other studies on imaging biomarkers, in which the image processing procedures under evaluation typically still have been at development stage (10,14,15). The region of interest from which the PET score is being derived had been identified in the original cross-sectional sample by the correlation of those voxels with MMSE (11), thus making its construction well suited for monitoring of disease progression. The robustness of the procedure has also been demonstrated previously in additional cross-sectional samples (12,16). We are therefore confident that the estimate of the variance associated with the PET score measurements described in the present paper is representative for the general application of the technique.

The PET score fulfills several requirements for qualification as a biomarker, as requested by regulators (17). As demonstrated in the present study, PET score provides an objective measure and has a high test–retest reliability, allowing for the assessment of treatment efficacy in a single patient. PET score is representative for the stage of the prodromal and early AD, at which drugs supposed to modify progression should exert their maximum effect. By being closely related to synaptic density and function (18,19), PET score is representative of the supposed mechanism of action of the drug that acts by preserving and maintaining synaptic function while being generic with respect to any molecular mechanisms that might be engaged in this action. As with all biomarkers, the relation to the desired clinical outcome, for example, prevention of cognitive impairment in AD, still needs to be clearly estab-

lished. Ideally, the evidence would include 2 positive phase 3 trials in which PET scores corresponded with clinical outcomes, but cumulative evidence from correspondence between clinical and PET outcomes in phase 2 trials might be considered as a more realistic pathway (3).

The increase of study power provided by PET scores is primarily based on their lower measurement variability, particularly obvious in stable healthy controls, for whom the coefficient-of-measurement variation for test–retest within 6 mo was only 16%, less than half of that for ADAS-cog, with excellent reliability at an intraclass correlation coefficient of 0.922, compared with 0.472 for ADAS-cog. In an actual clinical trial, the signal change due to clinical disease progression and the associated variation have to be considered, and both tend to increase with trial duration. Thus, a high accuracy of the measured outcome parameter is of particular importance in short-duration trials and at early stages of AD when the biologic signal change is relatively small. Correspondingly, PET scores provided a substantial increase in signal strength in MCI, whereas in AD a clear
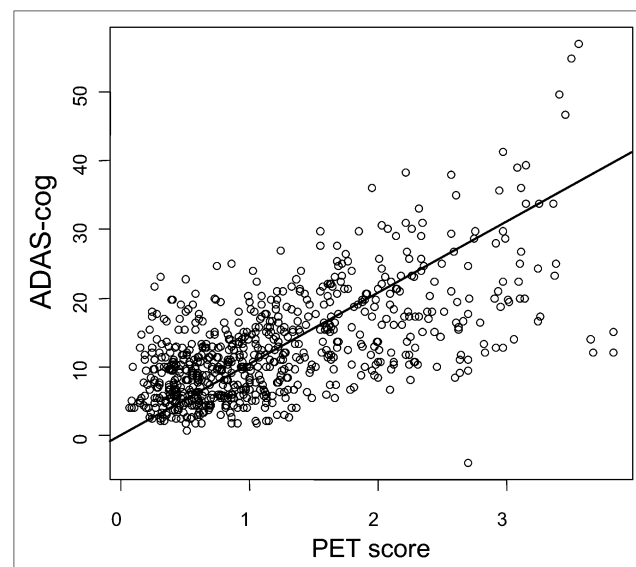
FIGURE 3. Scatterplot of corresponding ADAS-cog and PET scores with IV regression line.

TABLE 7
Changes Relative to Baseline in Entire Sample with Calibration of PET Scores to ADAS-cog Scale, Signal Strength, and Relative Required Sample Sizes in Clinical Trials

Variable	Mean	SD	Variance	Cohen d	Sample size*
Change at 6 m					
PET	0.581	2.468	6.092	0.236	120
ADAS	0.466	3.589	12.883	0.130	397
Change at 12 m					
PET	1.318	2.713	7.358	0.486	28
ADAS	1.167	4.510	20.339	0.259	100
Change at 24 m					
PET	2.768	3.841	14.755	0.721	13
ADAS	2.622	5.981	35.773	0.438	35

*Relative to 12-mo study using ADAS-cog (set to $n = 100$).

increase was present only after 6 mo (Cohen d in Table 3). At 12 and 24 mo in AD patients, the signal change due to biologic progression and its associated variation probably dominated over measurement-related variation, resulting in similar signal strength for PET scores and ADAS-cog.

^{18}F-FDG PET has been used in several clinical trials of AD in the past. In most of these trials the emphasis was on examining whether the drug would increase cerebral glucose metabolism as a pharmacodynamic effect of treatment rather than on assessment of progression. Typically these were short trials of a few weeks or up to 3 mo active treatment duration with ^{18}F-FDG PET before and during treatment (20–22). Trials that were extended for at least 6 mo also showed evidence of disease progression by further reduction of glucose metabolism in association cortices (23–26). However, these trials had not been designed to assess progression. For demonstration of a disease-modifying effect, ^{18}F-FDG PET should be treated like other functional measures. It may therefore require specific trial design, such as slope analysis, randomized start, or randomized withdrawal, which are currently being explored (27–29). There is also the potential for PET to be used as a sensitive and highly reproducible outcome measure in presymptomatic subjects who are at high genetic risk for developing AD (30).

^{18}F-FDG PET as a technical procedure that is independent of language and educational and cultural background may offer an advantage especially in studies performed across multiple countries. Future studies should clarify whether ^{18}F-FDG PET could also monitor progression in noncognitive domains, such as behavior. Clinical studies demonstrating metabolic impairment in the prefrontal cortex in the behavioral type of frontotemporal dementia (31) suggest that this is a realistic possibility.

MRI morphometry is another promising imaging biomarker for diagnosis and monitoring of progression (6), and a substantial increase of power, compared with ADAS-cog, has been demonstrated (15,32). In contrast to ^{18}F-FDG PET, results are based entirely on structural imaging and therefore are not influenced by actual synaptic function and pharmacodynamic effects, which facilitates the separation of progression from these functional effects. However, local brain volume may be biased by other confounding factors unrelated to disease progression, such as hydration and nutrition status (33). Thus, MRI morphometry and ^{18}F-FDG PET should be used as complementary biomarkers to assess structural and functional changes in a comprehensive manner, and that perspective could become particularly comfortable to patients when provided simultaneously in PET/MRI scanners (34).

Amyloid PET offers superior molecular specificity directly related to a major histopathologic marker of AD that has accumulated for many years before actual onset of dementia (35). However, it is currently unclear whether disease progression would be associated with further increase of tracer binding. Initial follow-up studies indicated that there is little further increase after onset of dementia (36), but recent preliminary results from large multicenter studies (ADNI, Australian Imaging, Biomarkers and Lifestyle) indicate further increase. A decrease of Pittsburgh compound B binding has been observed in patients undergoing clinical trials of drugs that remove amyloid from brain (37), but it has not yet been demonstrated that this would be associated with clinical benefit. Amyloid PET also is clearly complementary to functional assessment because its relation to cognitive deficits is rather weak and can usually be demonstrated only when including amyloid-negative subjects who probably do not have AD at any stage (38).

CONCLUSION

Our analysis demonstrates the validity of ^{18}F-FDG PET scores as an imaging biomarker for clinical trials to prevent dementia in MCI patients. Longitudinal ADNI data indicate that PET scores provide much higher test–retest reliability than ADAS-cog, which is the most frequently used as an outcome measure in dementia trials. By having a close and largely linear relation to ADAS-cog scores, PET scores also provide a valid measure of cognitive impairment. As a measure of disease progression, PET scores may provide a power

for 1-y studies in MCI patients similar to what they provide for 2-y studies based on progression of ADAS-cog scores.

DISCLOSURE STATEMENT

ACKNOWLEDGMENTS

REFERENCES

1. Aisen PS, Andrieu S, Sampaio C, et al. Report of the task force on designing clinical trials in early (predementia) AD. *Neurology.* 2011;76:280–286.
2. Vellas B, Andrieu S, Sampaio C, Coley N, Wilcock G. Endpoints for trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol.* 2008;7: 436–450.
3. Hampel H, Frank R, Broich K, et al. Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. *Nat Rev Drug Discov.* 2010;9:560–574.
4. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol.* 1997;42:85–94.
5. Herholz K. Cerebral glucose metabolism in preclinical and prodromal Alzheimer's disease. *Expert Rev Neurother.* 2010;10:1667–1673.
6. Fox NC, Kennedy J. Structural imaging markers for therapeutic trials in Alzheimer's disease. *J Nutr Health Aging.* 2009;13:350–352.
7. Haxby JV, Grady CL, Koss E, et al. Longitudinal study of cerebral metabolic asymmetries and associated neuropsychological patterns in early dementia of the Alzheimer type. *Arch Neurol.* 1990;47:753–760.
8. Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM. Longitudinal PET evaluation of cerebral metabolic decline in dementia: a potential outcome measure in Alzheimer's disease treatment studies. *Am J Psychiatry.* 2002;159:738–745.
9. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging.* 2011;32:1207–1218.
10. Chen K, Langbaum JB, Fleisher AS, et al. Twelve-month metabolic declines in probable Alzheimer's disease and amnestic mild cognitive impairment assessed using an empirically pre-defined statistical region-of-interest: findings from the Alzheimer's Disease Neuroimaging Initiative. *Neuroimage.* 2010;51:654–664.
11. Herholz K, Salmon E, Perani D, et al. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. *Neuroimage.* 2002;17:302–316.
12. Haense C, Herholz K, Jagust WJ, Heiss WD. Performance of FDG PET for detection of Alzheimer's disease in two independent multicenter samples (NEST-DD and ADNI). *Dement Geriatr Cogn Disord.* 2009;28:259–266.
13. Dunn G. Regression models for method comparison data. *J Biopharm Stat.* 2007;17:739–756.
14. Landau SM, Harvey D, Madison CM, et al. Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology.* 2010;75:230–238.
15. Hua X, Lee S, Yanovsky I, et al. Optimizing power to track brain degeneration in Alzheimer's disease and mild cognitive impairment with tensor-based morphometry: an ADNI study of 515 subjects. *Neuroimage.* 2009;48:668–681.
16. von Borczyskowski D, Wilke F, Martin B, et al. Evaluation of a new expert system for fully automated detection of the Alzheimer's dementia pattern in FDG PET. *Nucl Med Commun.* 2006;27:739–743.
17. Mani RB. The evaluation of disease modifying therapies in Alzheimer's disease: a regulatory viewpoint. *Stat Med.* 2004;23:305–314.
18. Hyder F, Patel AB, Gjedde A, Rothman DL, Behar KL, Shulman RG. Neuronal-glial glucose oxidation and glutamatergic-GABAergic function. *J Cereb Blood Flow Metab.* 2006;26:865–877.
19. Rocher AB, Chapon F, Blaizot X, Baron JC, Chavoix C. Resting-state brain glucose utilization as measured by PET is directly related to regional synaptophysin levels: a study in baboons. *Neuroimage.* 2003;20:1894–1898.
20. Heiss WD, Hebold I, Klinkhammer P, et al. Effect of piracetam on cerebral glucose metabolism in Alzheimer's disease as measured by positron emission tomography. *J Cereb Blood Flow Metab.* 1988;8:613–617.
21. Nordberg A, Lilja A, Lundqvist H, et al. Tacrine restores cholinergic nicotinic receptors and glucose metabolism in Alzheimer patients as visualized by positron emission tomography. *Neurobiol Aging.* 1992;13:747–758.
22. Mega MS, Dinov ID, Porter V, et al. metabolic patterns associated with the clinical response to galantamine therapy: a fludeoxyglucose F ^{18} positron emission tomographic study. *Arch Neurol.* 2005;62:721–728.
23. Heiss WD, Kessler J, Mielke R, Szelies B, Herholz K. Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease: a neuropsychological, EEG, and PET investigation. *Dementia.* 1994;5:88–98.
24. Tune L, Tiseo PJ, Ieni J, et al. Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer disease: results of a 24-week, double-blind, placebo-controlled study. *Am J Geriatr Psychiatry.* 2003;11:169–177.
25. Stefanova E, Wall A, Almkvist O, et al. Longitudinal PET evaluation of cerebral glucose metabolism in rivastigmine treated patients with mild Alzheimer's disease. *J Neural Transm.* 2005;112:29–44.
26. Tzimopoulou S, Cunningham VJ, Nichols TE, et al. A multi-center randomized proof-of-concept clinical trial applying [^{18}F]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease. *J Alzheimers Dis.* 2010;22:1241–1256.
27. Knopman DS. Clinical trial design issues in mild to moderate Alzheimer disease. *Cogn Behav Neurol.* 2008;21:197–201.
28. Vellas B, Andrieu S, Sampaio C, Wilcock G. Disease-modifying trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol.* 2007;6:56–62.
29. Ploeger BA, Holford NH. Washout and delayed start designs for identifying disease modifying effects in slowly progressive diseases using disease progression analysis. *Pharm Stat.* 2009;8:225–238.
30. Reiman EM, Langbaum JB, Tariot PN. Alzheimer's prevention initiative: a proposal to evaluate presymptomatic treatments as quickly as possible. *Biomark Med.* 2010;4:3–14.

31. Foster NL, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain.* 2007; 130:2616–2635.

32. McEvoy LK, Edland SD, Holland D, et al. Neuroimaging enrichment strategy for secondary prevention trials in Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2010;24:269–277.

33. Zivadinov R. Steroids and brain atrophy in multiple sclerosis. *J Neurol Sci.* 2005;233:73–81.

34. Judenhofer MS, Wehrl HF, Newport DF, et al. Simultaneous PET-MRI: a new approach for functional and morphological imaging. *Nat Med.* 2008;14: 459–465.

35. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging.* 2010;31:1275–1283.

36. Engler H, Forsberg A, Almkvist O, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. *Brain.* 2006;129:2856–2866.

37. Rinne JO, Brooks DJ, Rossor MN, et al. 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol.* 2010;9:363–372.

38. Edison P, Archer HA, Hinz R, et al. Amyloid, hypometabolism, and cognition in Alzheimer disease: an [11C]PIB and [18F]FDG PET study. *Neurology.* 2007;68:501–508.

Evaluation of a Calibrated ^{18}F-FDG PET Score as a Biomarker for Progression in Alzheimer Disease and Mild Cognitive Impairment

Karl Herholz, Sarah Westwood, Cathleen Haense and Graham Dunn

This article and updated information are available at:
http://jnm.snmjournals.org/content/52/8/1218

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

SOCIETY OF
NUCLEAR MEDICINE
AND MOLECULAR IMAGING