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Theoretical Impact of Florbetapir (^{18}F) Amyloid Imaging on the Diagnosis of Alzheimer's Dementia and the Detection of Preclinical Cortical Amyloid

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Abstract

In 2012, florbetapir (^{18}F) (Amyvid) received US FDA approval as a diagnostic agent for detecting neuritic (β-amyloid) plaques in live patients. Although such approval is specifically not extended to the usage of florbetapir as a single definitive diagnostic test for Alzheimer disease dementia (ADD), it is of considerable importance to examine its potential in this regard. To estimate the ability of florbetapir amyloid imaging to detect specified densities of postmortem-identified neuritic plaques, we used the data of Clark et al (2012). We then used the data of Beach et al (2012), derived from the National Alzheimer's Coordinating Center (NACC), to estimate the fraction of subjects that would have been called florbetapir-positive, and, of these, the fraction that would also meet neuropathological criteria for the presence of ADD. The accuracy of a positive florbetapir β-amyloid scan for the detection of neuropathologically defined ADD is estimated at between 69%–95% sensitivity and 83%–89% specificity. From the same NACC dataset, 144 subjects were recorded as having normal cognition; of these, 84 (58%) had at least sparse neuritic plaques at autopsy, and of these, it is estimated that florbetapir imaging would detect 47 (56%). These findings suggest that amyloid imaging may significantly improve the clinical identification of ADD.

Keywords

Alzheimer disease; Amyloid imaging; Autopsy; Dementia; Diagnosis; Neuropathology; Sensitivity; Specificity; Therapy

INTRODUCTION

The relative inaccuracy of the clinical diagnosis of Alzheimer disease dementia (ADD) may be a major impediment to clinical trials of candidate therapeutic agents (1). A recent study found sensitivity ranged from 70.9% to 87.3% while specificity ranged from 44.3% to

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70.8% depending on the confidence levels of the clinical and neuropathological criteria (2). When employing “clinically probable” ADD as the clinical diagnosis (3), and the combination of moderate or frequent cortical Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque densities with Braak neurofibrillary stage III-VI as the neuropathological definition (4) (the most commonly accepted clinical and neuropathological criteria over the time period examined), sensitivity and specificity were both only approximately 71%. For estimated drug effect sizes under 50%, such diagnostic inaccuracy would require at least a doubling of subject number to achieve sufficient statistical power for an adequate clinical trial. If the diagnostic inaccuracy is ignored, the clinical trial would likely be seriously underpowered. Improving the diagnostic accuracy would allow clinical trials with smaller subject numbers at lower cost, thereby expediting the discovery of new efficacious agents.

Current data suggest that early treatment of Alzheimer disease (AD) may be more likely to prevent irreversible brain damage, including synaptic loss and neuronal loss. In fact, it may be best to begin such preventative treatment at the preclinical stage of AD, when the pathophysiological disease processes have commenced but the disease is not yet clinically manifest (5). This preclinical stage is thought to extend over 1 to 2 decades or more (6), with neocortical β-amyloid biochemical and histological accumulation thought to be the first AD-specific alteration (7–11). Therefore, it may be critical to identify cortical β-amyloid deposition as early as possible to facilitate early prevention trials.

Imaging β-amyloid in living subjects offers the promise of assisting with both of these objectives. The separation of demented subjects with and without significant cortical β-amyloid deposits should allow the rejection of the diagnosis of ADD in subjects with a negative β-amyloid scan, and the identification of cortical β-amyloid deposits in cognitively normal older subjects should allow the selection of subjects for prevention trials who are in the preclinical stage of AD. A quantitative estimate of the potentialities and limitations of β-amyloid imaging, with respect to these objectives using neuropathologically defined ADD as the gold standard, has been lacking and is the subject of the present communication. To estimate the ability of florbetapir amyloid imaging to detect specified densities of postmortem-identified neuritic plaques, we used data derived from a published study of 59 subjects who received antemortem amyloid imaging with florbetapir followed by death, autopsy and histopathological evaluation (12). We then used the data from an autopsy study of 919 subjects, derived from the National Alzheimer's Coordinating Center (NACC) (2), to estimate the fraction of subjects that would have been called florbetapir-positive, and, of these, the fraction that would also meet neuropathological criteria for the presence of ADD.

MATERIALS AND METHODS

Florbetapir Imaging Subjects

Subjects were derived from those described in a previous publication, where details of the recruitment, imaging, tissue processing, and analytic methodology are described (12,13). Briefly, patients near the end of their lives were recruited from hospice, long-term care and community healthcare facilities for florbetapir-PET scanning. The inclusion and exclusion criteria were 1) a physician’s assessment that the individual was likely to die within 6

months of study, 2) the absence of any known destructive lesion in the brain (e g. stroke or tumor), and 3) the individual's willingness to have florbetapir imaging followed by a brain necropsy at the time of death. A flow chart (Figure 1 in the original publication; 13) schematically illustrates subject recruitment and analysis. One-hundred fifty-two subjects were injected with florbetapir; of these, 3 had invalid scans while 9 subjects or their legal representatives withdrew consent. Fifty-nine of the remaining 144 subjects who died within 2 years of imaging were autopsied and neuropathologically examined.

NACC Subjects

Data were derived from a NACC database search utilized in a prior publication (2). Subject data consisted of stipulated data elements from the NACC Uniform Data Set (UDS), obtained with the assistance of NACC personnel. The NACC UDS has been collected since September 2005 from more than 30 National Institute on Aging (NIA) Alzheimer's Disease Centers (ADCs) located throughout the United States. Most ADCs are at university medical centers in urban settings. Research subjects are generally recruited from the practices of participating neurologists with some additional community-based recruitment. The initial data pull included all 1198 subjects who had at least 1 UDS-compliant clinical assessment and then had died and were autopsied before September 2010. From this, 144 subjects were considered cognitively normal during life while 919 subjects had been diagnosed with dementia; 135 subjects were excluded for being diagnosed with mild cognitive impairment or because critical data fields were either not filled out or were marked "missing" or "not done". The clinical diagnosis of "dementia" or "cognitively normal" was that given at the last assessment during life.

Florbetapir-PET Imaging Methods

The details of the imaging methods have been previously described (12). Briefly, each subject underwent a 10-minute positron emission tomography (PET) scan at 50 minutes after receiving an intravenous bolus of 370 MBq (10 mCi) florbetapir F-18. Acquired PET scans were reconstructed either by iterative reconstruction with a post-reconstruction Gaussian filter or row action maximum likelihood algorithms to a 128 × 128 matrix with a zoom of 2.0–2.33. Florbetapir F18 PET images were assessed visually as either positive or negative by 5 board-certified nuclear medicine physicians blind to each other's readings and to all clinical and neuropathological data. For each reader, an intense level of tracer uptake in any single cortical region or a significant signal in any 2 cortical regions was sufficient to classify the entire scan as positive. For the present study, scan classification as positive or negative was determined in 2 ways: from the majority decision of the 5 readers and from the decision of the least accurate of the 5 readers (Reader 5).

Neuritic Plaque Density Quantification

At autopsy, brains from subjects imaged with florbetapir were processed with methods as previously described (12). Brains were fixed whole in 10% neutral-buffered formalin for 2 weeks prior to dissection. One set of tissue blocks was taken from the same cortical regions of interest as were used for imaging. These blocks were processed and embedded in paraffin and stained with a modified Bielschowsky silver method, as recommended by CERAD for the estimation of neuritic plaque density (14). Neuritic plaque density scores were obtained

from these sections by assigning values of none, sparse, moderate and frequent, according to the published CERAD templates (14). Identical methods are used by neuropathologists contributing to NACC.

Analysis Strategy

The goal of this analysis was first to ascertain the fraction of florbetapir study subjects at each of 4 histologically-defined CERAD neuritic plaque densities that were classified as positive by florbetapir imaging (12). As mentioned above, 2 estimates were used: 1 for the majority read of the 5 readers used in the original study and 1 for the least accurate of the 5 individual readers (Reader 5 of the original study). These estimates were then applied to the NACC data to indicate the fraction of demented subjects that would be correctly identified by a positive florbetapir scan as having neuropathologically confirmed ADD, with the latter defined as subjects having moderate or frequent cortical CERAD neuritic plaque densities as well as Braak neurofibrillary stage III-VI, roughly equivalent to NIA-Reagan “intermediate” or “high” levels of probability (4). Additionally, the fractions of subjects detected by florbetapir imaging at each of the defined CERAD neuritic plaque densities were used to estimate the fraction of cognitively normal subjects with at least sparse neuritic plaques that would have been identified by florbetapir imaging. For this calculation, only the majority read data were used. Sensitivity and specificity were calculated with no adjustments made for age, gender or other subject characteristics. Groups were compared with analysis of variance and Kruskall-Wallis analysis of variance. For all tests, the significance level was set at $p < 0.05$.

RESULTS

Florbetapir and NACC Subject Characteristics

Of 59 florbetapir study subjects autopsied after imaging, 46 had an autopsy within 12 months (mean 3.8 months) of their florbetapir scan while the other 13 died with mean elapsed scan to death duration of 16.3 months (Table 1). Forty-three subjects were demented and 16 were non-demented. For NACC subjects, the mean interval between last clinical assessment and death was 10.8 months. The subgroups of subjects (florbetapir and NACC, demented and non-demented) differed significantly in age but all subgroups were predominantly elderly, with mean ages ranging between 76.9 years and 86.4 years. For both subject sets, demented subjects had significantly greater neuritic plaque densities and Braak neurofibrillary stages than non-demented subjects but there were no significant differences in these measures between the florbetapir and NACC groups.

Ability of Florbetapir to Detect Defined CERAD Neuritic Plaque Densities

From the majority reads published in Clark et al (12), florbetapir scans were classified as negative in all 15 subjects found after death to have no cortical neuritic plaques as well as in all 5 subjects with sparse neuritic plaque densities. For subjects with moderate densities of neuritic plaques at autopsy, 10/13 (77%) were classified as florbetapir scan-positive during life while all 26 subjects with frequent neuritic plaques were florbetapir-positive. For the least accurate of the individual readers (Reader 5), 13/15 (86.7%) subjects with no postmortem cortical neuritic plaques were classified as negative; all 5 subjects with sparse

neuritic plaques were classified as positive; of those with moderate neuritic plaques, 9/13 (69.2%) were classified as positive while for those with frequent neuritic plaques, 18/26 (69.2%) were classified as positive.

Sensitivity and Specificity of Florbetapir Imaging for Neuropathologically Defined ADD

These calculations are based on usage of a florbetapir scan as the "test" for neuropathologically confirmed ADD, with the "gold standard" being the combination of CERAD moderate or frequent neuritic plaques as well as Braak neurofibrillary stage III-VI, as determined at autopsy. Because the subjects that received the florbetapir scan are an entirely different set from those that received autopsy, the results can only be an approximate and theoretical estimate. The fraction of NACC subjects, from the study of Beach et al (2), that would be correctly diagnosed as ADD by a florbetapir-positive scan was calculated based on the fraction of subjects at moderate or frequent CERAD neuritic plaque density that would be expected to be florbetapir-positive based on the data of Clark et al (12), and on the fraction of these that would also have Braak stage of III-VI, from the data of Beach et al (2). The contingency table used for the calculation of sensitivity and specificity is shown as Table 2. For the majority read, sensitivity was thus calculated to be 95.1% and specificity was 89.4%. For the least accurate reader, sensitivity was 69.1% and specificity was 83.0%.

Subjects with a Positive Florbetapir Scan but Neuropathologically not ADD

From the majority read florbetapir detection rates calculated for differing CERAD neuritic plaque densities (12) and the NACC data (2), of 520 subjects expected to be positive on florbetapir imaging, 32 (5.2%) would be expected not to meet the neuropathological definition of ADD as defined for this study (Table 2) due to having a Braak neurofibrillary stage less than III. Such subjects would be "false positives" if a florbetapir scan were used as the sole criterion for the diagnosis of ADD. The diagnostic composition of such subjects can be inferred from the total number of subjects in the NACC demented subject set (n = 919) that have moderate or frequent CERAD neuritic plaque densities but a Braak stage less than III. There were 38/919 NACC subjects (4.1%) in this category. Their neuropathological diagnoses are shown in Table 3. There were 9 NACC subjects that had received the primary neuropathological diagnosis of AD but did not meet the present study definition of ADD because they had a Braak stage less than III. Twelve subjects had frontotemporal lobar degeneration of several types; the diagnostic breakdown of these subjects is given in Table 4. Eleven subjects had Lewy body disease thought sufficient to have caused dementia. One subject had hippocampal sclerosis (and an additional 3 subjects with hippocampal sclerosis were classified under the frontotemporal lobar degeneration category) (Table 4). One subject had progressive supranuclear palsy and 2 subjects had AD pathology present but insufficient for diagnosis. One case was diagnosed only as "extreme depopulation of substantia nigra" and one was found to be neuropathologically normal.

Detection of Preclinical Cortical β-Amyloid Deposits with Florbetapir Imaging

Of the 144 NACC subjects classified as having been cognitively normal during life, 84 (58%) had neuritic plaques, ranging in density from sparse to frequent (Table 5). From the majority read florbetapir detection rates calculated for differing CERAD neuritic plaque

densities (12), it is expected that 47/144 NACC cognitively normal subjects (32.6 %) would have had a positive florbetapir scan. Approximately 37 subjects would be "false negative" for cortical β-amyloid because they would have had at least sparse neuritic plaques at autopsy but would have been florbetapir scan-negative. Expressed another way, 47/84 (56%) of cognitively normal subjects with at least sparse neuritic plaques would have been detected by florbetapir imaging. Additional subjects with frequent or moderate diffuse plaques but sparse or no neuritic plaques might or might not be detected but as there are no reliable data for the sensitivity of florbetapir or other β-amyloid imaging agents for the presence of diffuse plaques, we did not consider these.

DISCUSSION

Based on the results of 2 studies (2,12), we have calculated the theoretical sensitivity and specificity of a positive brain β-amyloid imaging scan with florbetapir (^{18}F), if used as the sole diagnostic criterion, for the presence of neuropathologically defined ADD. We have also calculated the theoretical fraction of non-demented subjects with cortical β-amyloid that would be detected with a florbetapir scan. For the definition of neuropathologically confirmed ADD we used the combination of CERAD moderate or frequent neuritic plaque density together with Braak neurofibrillary stage III-VI. This is equivalent to an intermediate or high probability under the NIA-Reagan classification system (4), which was generally accepted as the neuropathological "gold standard" for the diagnosis of dementia due to AD between 1997 and 2012. Updated neuropathological criteria were published in 2012 under the sponsorship of the NIA and the Alzheimers' Association (NIA-AA criteria) (15), but we were not able to apply these because the NACC data used in the present study were collected between 2005 and 2010, before the NIA-AA criteria were published. Also, the contributing NIA-ADCs were not using the Thal β-amyloid phasing system (16), which is required as part of the new criteria. In order to meet their respective intermediate or high levels, both the NIA-Reagan and NIA-AA criteria stipulate a Braak neurofibrillary stage greater than II, however. Therefore, the case proportion determined in the present study to be "false-positive" on florbetapir imaging, because of the presence of moderate or frequent CERAD neuritic plaque densities but a Braak stage less than III, would be the same under both sets of criteria.

Neuritic plaques were first defined based on ultrastructural criteria by Wisniewski and Terry (17), but our usage of the term is necessarily that of Mirra et al (14) as both of the publications on which the present study is based used the CERAD definition of neuritic plaques. Although not informative with respect to molecular composition, the CERAD definition of neuritic plaques as particular morphological entities has the great advantages of being sufficiently unambiguous to result in relatively high inter-observer agreement (18,19); moreover, there is a wealth of studies that have assess its clinicopathological significance. The adoption of the CERAD definition of neuritic plaques by the NIA ADCs enabled the accumulation of statistically large autopsied subject numbers that had all been assessed with relatively equivalent methods. This led to the confirmed realization that neuritic plaques have a significant association with dementia and cognitive impairment whereas diffuse plaques generally do not (20). The revised NIA-Alzheimer's Association recommendations for the neuropathological assessment of AD include Thal-Braak staging of β-amyloid

plaques, defined as any plaque type that is immunoreactive for β-amyloid, as one arm of the tripartite histological assessment (15, 21); the accumulation of sufficient postmortem data will allow a test of whether brain regional plaque distribution is also an important predictor of clinical status. At the present time, however, immunohistochemical staining for β-amyloid has been judged to be poorly suited for the subtyping of plaques or for the grading of plaque density (22). The 2 publications from the Avid study included analyses of quantitative florbetapir imaging compared with quantitative β-amyloid immunohistochemistry as well as Bielschowsky silver method-obtained neuritic plaque density estimates and found both staining methods to have strong and significant correlations with each other and with florbetapir uptake (12, 13).

The diagnostic capability of a positive florbetapir β-amyloid PET scan for the presence of neuropathologically confirmed ADD (as defined in this study) is estimated here at between 69% and 95% sensitivity and between 83% and 89% specificity. The scans classified by a majority read of a panel of 5 readers may represent an approximation of the upper limit of attainable accuracy while the single read by the least accurate reader may be a reasonable approximation of the lower limits of accuracy. Using data from the single most accurate reader (Reader 4), the calculated sensitivity and specificity was equivalent to the majority read (calculations not shown). Either set of figures is, however, a significant improvement over the 71% sensitivity and 71% specificity obtained in the setting of academic cognitive neurology practices utilizing clinical examination and standard diagnostic modalities (but excluding β-amyloid imaging and other experimental biomarker studies), such as those in the US NIA-ADCs (2). The use of florbetapir imaging or other comparable β-amyloid imaging agents would appear, therefore, to improve diagnostic accuracy significantly and hence subject selection for ADD clinical trials, thereby allowing smaller subject numbers and lower trial costs. More accurate diagnosis would also limit undesirable clinical consequences that may result from the misclassification of demented subjects (23).

It is important to recognize, however, that the sensitivity and specificity figures calculated here are not generalizable to all settings or populations. We specifically limited our study to subjects that had already been clinically diagnosed with dementia. The florbetapir study had a relatively small sample size and this may have affected the accuracy of the estimate of the ability of florbetapir to detect defined neuritic plaque density levels. Both the subjects in the Avid study and those in the NACC database are mostly derived from specialized dementia clinics and it is possible that even the control subjects may have been enriched in individuals at higher risk for AD. Both sets of subjects were predominantly composed of those with end-stage dementia and thus are not representative of the usual community population of elderly or the usual dementia clinic population. It is likely that the predictive power of a positive florbetapir scan for ADD would be much lower if the setting had been a random sample of both non-demented and demented elderly subjects from a community-based cohort, due to the presence of significant cortical β-amyloid in many non-demented subjects (24). Studies will need to be done in more socially and economically diverse populations in order to determine whether this might be true. Nonetheless, the present data suggest that in the setting of an established dementia, the sensitivity and specificity of a florbetapir scan for the presence of clinically significant AD is likely to be significantly more accurate than what

it would be using standard neurological practices alone. This has important implications for both clinical trials and medical practice.

Our calculations also show that florbetapir imaging may detect 56% of no demented subjects with cortical neuritic plaques. This is encouraging but demonstrates that the very earliest stages of what might be termed “preclinical AD” (when there may be only sparse densities of cortical neuritic plaques) are still expected to be mostly or entirely florbetapir-negative, at least when using equivalent scan analysis methods as were used in the florbetapir trial. Only more advanced preclinical AD subjects, predominantly those that harbor moderate or frequent neuritic plaques, are likely to be identified. It is possible, however, that if the objective was to identify sparse densities of cortical neuritic plaques, that other, more sensitive ligands, or other more sensitive qualitative or quantitative scan analysis methods, could be developed to do this. It is also possible that the necessary interval in the florbetapir study between scanning and death resulted in an underestimate of the ability of florbetapir to detect sparse plaques due to the progression of β-amyloid deposition during this interval. A longer scan-death interval had, however, only a slight effect on florbetapir sensitivity, as previously reported (12).

Although β-amyloid imaging is thus expected to increase the clinical diagnostic accuracy for the presence of ADD, there is much heterogeneity within this diagnosis that is still generally undetectable during life and might be expected to affect clinical trial response rates (25). At present there are no imaging agents for neurofibrillary tangles or pathological tau protein aggregates and, therefore, we cannot place any particular living ADD subject into their Braak neurofibrillary stage. It is likely that subjects in Braak stage III or IV, when tangles are limited to the limbic system, will be easier to treat than subjects in Braak stage V or VI, when tangles have spread throughout the neocortex. In many or even most subjects with ADD, 1 or more additional major neuropathological diagnoses are present, such as vascular dementia, dementia with Lewy bodies, hippocampal sclerosis dementia, progressive supranuclear palsy and others. Nevertheless, the increased diagnostic accuracy offered by florbetapir imaging is likely to have a beneficial impact on the efficiency of ADD clinical trials. Increased diagnostic accuracy might also result in improved treatment for AD and non-AD dementias (23).

An important consideration is that the FDA has specifically directed that florbetapir be used only as a diagnostic aid, along with a standard clinical diagnostic work-up, rather than as a sole diagnostic agent for ADD. These results are not intended as a recommendation that florbetapir scanning be used as a sole diagnostic test for ADD. Nevertheless, due to the potentially large improvements in diagnostic accuracy and clinical trial efficacy that might be obtained with florbetapir and similarly-effective β-amyloid imaging agents, we felt it important to explore this potential with the current study.

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manuscript. TGB has also received institutional funding for a separate, more recent study funded by Avid/Lilly, and, additionally, has received institutional funding for participating in amyloid imaging studies funded by Bayer Healthcare together with Piramal Healthcare, GE Healthcare and Navidea Biopharmaceuticals, and has served as a personally remunerated consultant to GE Healthcare.

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REFERENCES

1. Beach TG. Alzheimer's disease and the "Valley Of Death": not enough guidance from human brain tissue? J Alzheimers Dis. 2013; 33(Suppl 1):S219–S233. [PubMed: 22695622]
2. Beach TG, Monsell SE, Phillips LE, et al. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. J Neuropathol Exp Neurol. 2012; 71:266–273. [PubMed: 22437338]
3. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
4. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Neurobiol Aging. 1997; 18:S1–S2. [PubMed: 9330978]
5. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:280–292. [PubMed: 21514248]
6. Duyckaerts C, Hauw JJ. Prevalence, incidence and duration of Braak's stages in the general population: can we know? Neurobiol Aging. 1997; 18:362–369. [PubMed: 9380250]
7. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010; 9:119–128. [PubMed: 20083042]
8. Ingelsson M, Fukumoto H, Newell KL, et al. Early Abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. Neurology. 2004; 62:925–931. [PubMed: 15037694]
9. Funato H, Yoshimura M, Kusui K, et al. Quantitation of amyloid beta-protein (A beta) in the cortex during aging and in Alzheimer's disease. Am J Pathol. 1998; 152:1633–1640. [PubMed: 9626067]
10. Davies L, Wolska B, Hilbich C, et al. A4 amyloid protein deposition and the diagnosis of Alzheimer's disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques. Neurology. 1988; 38:1688–1693. [PubMed: 3054625]
11. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013; 12:207–216. [PubMed: 23332364]
12. Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. Lancet Neurol. 2012; 11:669–678. [PubMed: 22749065]
13. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA. 2011; 305:275–283. [PubMed: 21245183]
14. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991; 41:479–486. [PubMed: 2011243]
15. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012; 123:1–11. [PubMed: 22101365]
16. Thal DR, Rüb U, Orantes M, et al. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002; 58:1791–1800. [PubMed: 12084879]

17. Wisniewski HM, Terry RD. Reexamination of the Pathogenesis of the Senile Plaque. 1973:4–26.
18. Mirra SS, Gearing M, McKeel DW Jr, et al. Interlaboratory comparison of neuropathology assessments in Alzheimer's disease: a study of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). J Neuropathol Exp Neurol. 1994; 53:303–315. [PubMed: 8176413]
19. Halliday G, Ng T, Rodriguez M, et al. Consensus neuropathological diagnosis of common dementia syndromes: testing and standardising the use of multiple diagnostic criteria. Acta Neuropathol. 2002; 104:72–78. [PubMed: 12070667]
20. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer Disease Neuropathologic Changes With Cognitive Status: A Review of the Literature. J Neuropathol Exp Neurol. 2012; 71:362–381. [PubMed: 22487856]
21. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. 2012; 8:1–13. [PubMed: 22265587]
22. Alafuzoff I, Pikkarainen M, Arzberger T, et al. Inter-laboratory comparison of neuropathological assessments of beta-amyloid protein: a study of the BrainNet Europe consortium. Acta Neuropathol. 2008; 115:533–546. [PubMed: 18343933]
23. Gaugler JE, Ascher-Svanum H, Roth DL, et al. Characteristics of patients misdiagnosed with Alzheimer's disease and their medication use: an analysis of the NACC-UDS database. BMC Geriatr. 2013; 13:137. [PubMed: 24354549]
24. Chetelat G, La JR, Villain N, et al. Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. Neuroimage Clin. 2013; 2:356–365. [PubMed: 24179789]
25. Dugger BN, Clark CM, Serrano G, et al. Neuropathologic heterogeneity does not impair florbetapir-positron emission tomography postmortem correlates. J Neuropathol Exp Neurol. 2014; 73:72–80. [PubMed: 24335535]

Table 1

Amyloid imaging and National Alzheimer's Coordinating Center Patient Characteristics

Clinical Diagnosis	Mean Age ± SD (y)	Gender	Median Neuritic Plaque Density (range)	Median Braak Stage (range)
Amyloid Imaging Subjects				
Demented (N = 43)	81.2 ± 11.1	34M / 25F	3 (0–3)	5 (2–6)
Non-Demented (N = 16)	76.9 ± 16.0	11M / 5F	0 (0–3)	2 (0–4)
NACC Subjects				
Demented (N = 919)	79.0 ± 11.4	551M / 368F	3 (0–3)	5 (0–6)
Non-Demented (N = 144)	86.4 ± 8.8	65M / 79F	1 (0–3)	2 (0–6)

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; F, female; M, male; NACC, National Alzheimer's Coordinating Center, University of Washington, Seattle, WA.

Table 2

Contingency Tables for Derivation of the Theoretical Sensitivity and Specificity of a Positive Florbetapir Amyloid Scan For the Presence of Neuropathologically Confirmed Alzheimer Disease Dementia

Majority Read	**NP density moderate or frequent and Braak stage III-VI N = 618**	**NP density none or sparse and/or Braak stage 0-II N = 301**
Florbetapir amyloid scan positive (N = 620)	a) N = 588	b) N = 32
Florbetapir amyloid scan negative (N = 299)	c) N = 30	d) N = 269
	Sensitivity = 95.1%	Specificity = 89.4%
Least Accurate Reader	NP density moderate or frequent Braak stage III-VI N = 618	NP density none or sparse Braak stage 0-II N = 301
Florbetapir amyloid scan positive N = 565	a) N = 427	b) N = 51
Florbetapir amyloid scan negative N = 354	c) N = 191	d) N = 250
	Sensitivity = 69.1%	Specificity = 83.0%

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NACC, National Alzheimer's Coordinating Center, University of Washington, Seattle, WA

The presence of neuropathologically confirmed Alzheimer disease dementia is defined as the presence of moderate or frequent CERAD cortical neuritic plaque (NP) density and Braak neurofibrillary stage III-VI. Two separate calculations are shown. One uses the results from the majority read of florbetapir scans; the other uses results from the least accurate of the 5 readers. Sensitivity is calculated as the ratio of a/(a + c); specificity is calculated as d/(b + d).

Table 3

Primary Neuropathological Diagnoses for the 38 National Alzheimer's Disease Coordinating Center Subjects with Moderate or Frequent Neuritic Plaque Densities But Not Meeting Neuropathological Definition of Alzheimer Disease

Primary Neuropathological Findings	Number of subjects
Primary neuropathological diagnosis of AD despite low level of AD histopathology	9
Frontotemporal lobar degeneration	12
Lewy body disease	11
Hippocampal sclerosis	1
Progressive supranuclear palsy	1
AD pathology present but insufficient for diagnosis	2
“Extreme depopulation of substantia nigra”	1
Normal brain	1

Subjects had moderate or frequent CERAD neuritic plaque densities but did not meet neuropathological definition of Alzheimer Disease because of a Braak neurofibrillary stage less than III (based on majority read data).

AD, Alzheimer disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NACC, National Alzheimer's Coordinating Center, University of Washington, Seattle, WA.

Table 4

Subtype of Neuropathological Diagnosis for 12 National Alzheimer's Coordinating Center Subjects with Frontotemporal Lobar Degeneration (FTLD) and Moderate or Frequent CERAD Neuritic Plaque Densities But Not Meeting Neuropathological Definition of Alzheimer Disease Dementia

Subtype of frontotemporal lobar degeneration	Number of subjects
Hippocampal sclerosis	3
Pick disease	2
FTLD with ubiquitin-positive, tau-negative inclusions	2
FTLD with tau-positive or argyrophilic inclusions	1
Tangle-predominant dementia or argyrophilic grain dementia	1
FTLD with no distinctive histology	1
FTLD with “lower motor neuron pathology”	1
Corticobasal degeneration	1

Subjects had moderate or frequent CERAD neuritic plaque densities but did not meet neuropathological definition of Alzheimer Disease because of a Braak neurofibrillary stage less than III (based on majority read data). See Table 3 for other diagnostic categories.

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; FTLD, frontotemporal lobar degeneration; NACC, National Alzheimer's Coordinating Center, University of Washington, Seattle, WA.

Table 5

Distribution of Neuritic Plaque Densities In 84 Cognitively Normal Subjects From The National Alzheimer's Coordinating Center Database With At Least Sparse Neuritic Plaques

Plaque type and density	Number of subjects
CERAD frequent neuritic plaques	16
CERAD moderate neuritic plaques	40
CERAD sparse neuritic plaques	28
No neuritic plaques	60

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NACC, National Alzheimer's Coordinating Center, University of Washington, Seattle, WA.