The pathologic hallmarks of Alzheimer disease (AD) are neurofibrillary tangles of hyperphosphorylated τ and extracellular plaques of β-amyloid (Aβ) proteins, which involve the brain many years before the emergence of symptoms. Molecular imaging with agents that bind to Aβ and τ proteins may detect the presence and progression of Alzheimer disease pathology during the preclinical stage when the disease course may be altered by early intervention. Imaging of the Aβ pathology with PET has been used in clinical research settings for almost a decade and was recently approved by the US Food and Drug Administration for clinical use. Imaging of τ pathology with PET has been investigated less; however, its impact on understanding the pathophysiology of AD and on treatment planning would be significant. Imaging of both Aβ and τ will likely contribute independently to early diagnosis, differential diagnosis, and the tracking of disease progression during the preclinical, prodromal, and clinical stages of AD.

Detecting Preclinical and Prodromal AD Pathology with Molecular Imaging

During the past decade, discovery of Aβ imaging with Pittsburgh compound-B (PiB) PET provided a window into the pathophysiology of AD in living individuals. Although postmortem studies have long suggested a high prevalence of Aβ pathology with moderate-to-frequent plaques reaching 47% in cognitively normal older adults, imaging of Aβ pathology with PET provided an in vivo confirmation of this observation. The prevalence of PiB positivity ranges from 20% to 34% in independent cohorts of cognitively normal individuals.2-6 The variability is likely associated with the ascertainment of participants and the cutoff used for PiB positivity as well as the median age of the cohorts. For example, in a population-based study of cognitively normal older adults that included individuals with neurologic, psychiatric, or systemic illnesses, a representative sample of the population, the prevalence of PiB positivity was 31% with a global cortical PiB uptake cutoff of >1.5, but the prevalence increased to 44% with a cutoff of >1.4, which is on par with the postmortem studies in community-based cohorts of cognitively normal elderly.8

Although Aβ pathology is common in cognitively normal individuals, the harmful effects of Aβ pathology on cognitive func-
Przybelski SA, et al. APOE modifies the association between Abeta load and cognition in preclinical Alzheimer disease (AD) and short-term progression rates. If one used the preclinical staging criteria, at fixed cut-points corresponding to 90% sensitivity for diagnosing AD and the 10th percentile of cognitive scores of cognitively healthy individuals, stage 0 corresponds to a low Aβ load on PET and the absence of imaging markers of neuronal injury (ie, normal hippocampal volumes on MR imaging and/or the absence of an AD-like pattern of hypometabolism on PET); stage 1 corresponds to a high Aβ load on PET and the absence of imaging markers of neuronal injury; stage 2 corresponds to a low Aβ load on PET, the presence of imaging markers of neuronal injury, and subtle cognitive impairment. The percentage of patients who progressed to mild cognitive impairment are modest. The risk of cognitive decline further increases with the Aβ load. The high Aβ load on PET appears to have subtle effects on memory, attention/executive function, and visual–spatial processing.

The relationship between Aβ load and cognitive domain functions does not appear to follow a specific functional-anatomic pattern but is localized to the frontal, lateral temporal, and parietal lobes; posterior cingulate; and precuneus cortex, independent of the cognitive domains that are affected. Therefore the effects of Aβ detected on PET appear to be global, and the APOE ε4 status further modifies the association between Aβ load and cognition. Although cognitively normal carriers of the APOE ε4 have higher Aβ loads on PET compared with noncarriers, when matched on Aβ load, APOE ε4 carriers tend to perform worse on cognitive tests compared with noncarriers (Fig 1). Thus, APOE ε4 not only increases the risk for Aβ deposition but also influences AD pathology by modulating the harmful effects of Aβ on cognitive function through other potentially synergistic mechanisms, such as enhancing hyperphosphorylation of the τ protein and reducing choline acetyltransferase activity.

In 2011, the clinical diagnostic criteria for AD were revised under the auspices of the National Institutes of Aging and the Alzheimer’s Association (NIA-AA). These new guidelines included imaging markers in the diagnostic criteria for AD and proposed research criteria that included imaging evidence of AD for the diagnosis of preclinical AD. The new criteria require evidence of Aβ pathology of AD for the diagnosis of preclinical AD either through molecular imaging or CSF biomarkers. Any imaging or biomarker evidence of AD-related neurodegeneration measured with an AD pattern of atrophy on MR imaging or an AD pattern of hypometabolism on [18F] fluorodeoxyglucose PET and the presence of subtle cognitive difficulties in addition to the Aβ pathology increase the stage of preclinical AD from 1 to 3.

The preclinical AD research criteria was operationalized in a population-based sample of cognitively normal older adults from the Mayo Clinic Study of Aging. At fixed cut-points corresponding to 90% sensitivity for diagnosing AD and the 10th percentile of cognitive scores of cognitively normal individuals, 43% of the sample was classified as stage 0; 16%, stage 1 (Aβ PET–positive); 12%, stage 2 (Aβ PET–positive and neurodegeneration-positive on MR imaging or FDG-PET); and 3%, stage 3 (Aβ PET–positive and neurodegeneration-positive on MR imaging or FDG-PET and subtle cognitive difficulties). Furthermore, the proportion of subjects who progressed to mild cognitive impairment (MCI) or dementia increased with advancing stage (Fig 2). However, 23% of the population did not fit the preclinical AD stages because they had normal Aβ PET imaging findings but abnormal neurodegeneration biomarker study findings, which we classified as suspected non-AD pathophysiology. The suspected non-AD pathophysiology group is of particular interest because the individuals progress to MCI in the short term (10% in 15 months), albeit at a rate similar to that of subjects with stage 1 preclinical AD (11% in 15 months). The pathologic basis of positive neurodegeneration biomarker findings in the absence of Aβ pathology in this cognitively normal group is under investigation.

According to the new guidelines by the NIA-AA, the prodromal stage of AD is characterized by mild cognitive impairment, and research criteria further classify patients with MCI as having MCI due to AD on the basis of biomarker evidence of AD pathophysiology. A recent study from the Mayo Clinic Study of Aging...
and Alzheimer Disease Neuroimaging Initiative demonstrated that the NIA-AA criteria apply to most subjects with MCI in both the community and clinical trial settings; however, a sizeable proportion of subjects had conflicting biomarkers, which need to be investigated.29 In this population, neurodegeneration on MRI increased the rate of progression to dementia in patients with MCI due to AD and appeared to be a key factor in predicting progression relative to Aβ deposition alone.

Molecular imaging studies with Aβ-binding ligands in preclinical AD indicate that approximately one-third of the population of cognitively normal individuals and 71% of patients with MCI in the community have high cortical Aβ loads. In cognitively normal individuals, high levels of Aβ deposition are associated with subtle cognitive deficits, cognitive decline, and a higher risk of cognitive impairments in the future. However, these relationships appear to be modified by the genetic markers,5,30 lifestyle activities,31 or cognitive reserve.32

**Molecular Imaging for the Differential Diagnosis of AD**

The high sensitivity and specificity of PiB binding to fibrillar Aβ have been demonstrated in vitro,33 in mouse models,34 and in human tissue.35 The newer [18F] agents for Aβ PET have undergone a similar validation process36–44 and appear to show properties similar to those of PiB.41–45 The specificity of PiB to fibrillar Aβ is preserved even in patients with protein deposits associated with other neurodegenerative dementias such as α-synuclein in dementia with Lewy bodies (DLB) (Fig 3).46–49 However, there may be disagreements between the postmortem report and the PET findings because of the heterogeneity of Aβ deposits. For example, PiB labels both neuritic and diffuse plaques, though labeling of diffuse/amorphous plaques is less prominent than that of compact/cored plaques.35,50 Patients with dementia with Lewy bodies or Parkinson disease dementia, who typically have high loads of diffuse plaques, may have positive Aβ PET scan findings but would not be classified as having AD because of the absence of fibrillar Aβ deposits need further investigation.

One of the key applications of Aβ PET imaging in clinical practice is in the differential diagnosis of AD. The accuracy of Aβ PET in distinguishing AD and frontotemporal lobar degeneration is quite high,55 with an overall classification accuracy of 97% in cases with histopathologic confirmation.56 On the other hand, the 2 most common dementia pathologies after AD are vascular disease and Lewy body pathologies, which commonly are present with additional AD pathology. In these cases, the presence of an intermediate-to-high Aβ load may be insufficient to determine the predominant pathology contributing to the dementia syndrome. In keeping with the postmortem data, 25%–35% of patients with vascular dementia57,58 and 60%–80% of patients with DLB54 and may be useful in predicting the presence of AD pathology in patients with DLB (Fig 4).60 Molecular imaging of the impaired nigrostriatal dopaminergic transmission in DLB with 2β-carbomethoxy-3β-(4-iiodophenyl)-N-(3-fluoropropyl) nortropane with SPECT64 or loss of monoaminergic terminal integrity with vesicular monoamine transporter type 2 radioligands may further detect the Lewy body–related pathologic features in cases with mixed dementia and may be complementary to Aβ PET.55

The added diagnostic value of Aβ PET imaging in the differential diagnosis of dementia across different clinical settings has become a topic of significant interest with the availability of [18F] agents for Aβ imaging.66–70 Although the added value of Aβ PET to clinical decision-making has not been established,66–69 how Aβ load is measured on PET scans (ie, visual evaluation versus various quantitative techniques) appears to make a difference in the value of this diagnostic technique in the clinical setting.69
cates that APOE presence of progression to AD appear to have the highest rates of Aβ deposition detected with molecular imaging and functional outcomes in patients with AD dementia. Similarly, it is expected that imaging of the τ pathology of AD, especially with agents specific to the τ pathology that are currently being developed and tested, will open avenues for development of new targets for prevention.

**REFERENCES**

1. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer’s disease with Pittsburgh compound-B. *Ann Neurol* 2004;55:306–19
2. Pike KE, Ellis KA, Villemagne VL, et al. Cognition and beta-amyloid in preclinical Alzheimer’s disease: data from the AIBL study. *Neuropsychologia* 2011;49:2384–90
3. Morris JC, Roe CM, Xiong C, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol* 2010;67:122–31

4. Aizenstein HJ, Neubes RD, Saxton JA, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol* 2008;65:1509–17

5. Kantarci K, Lowe V, Przybelski SA, et al. APOE modifies the association between Abeta load and cognition in cognitively normal older adults. *Neurology* 2012;78:232–40

6. Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol* 2012;72:578–86

7. Mielke MM, Wiste HJ, Weigand SD, et al. Indicators of amyloid burden in a population-based study of cognitively normal elderly. *Neurology* 2012;79:1570–77

8. Sonnen JA, Larson EB, Crane PK, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol* 2007;62:406–13

9. Pike KE, Savage G, Villemagne VL, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer’s disease. *Brain* 2007;130:2837–44

10. Chételat G, Villemagne VL, Pike KE, et al. Relationship between memory performance and beta-amyloid deposition at different stages of Alzheimer’s disease. *Neurol Degener Dis* 2012;10:141–44

11. Fagan AM, Mintun MA, Shah AR, et al. Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer’s disease. *EMBO Mol Med* 2009;1:371–80

12. Mormino EC, Kluth JT, Madison CM, et al. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain* 2009;132:1310–23

13. Doraiaiswamy PM, Sperling RA, Coleman RE, et al. Amyloid-beta assessed by florbetapir F 18 PET and 18-month cognitive decline: a multicenter study. *Neurology* 2012;79:1636–44

14. Chételat G, Villemagne VL, Pike KE, et al. Independent contribution of temporal beta-amyloid deposition to memory decline in the pre-dementia phase of Alzheimer’s disease. *Brain* 2011;134:798–807

15. Rentz DM, Amagirile RO, Becker JA, et al. Face-name associative memory performance is related to amyloid burden in normal elderly. *Neuropsychologia* 2011;49:2776–83

16. Rodrigue KM, Kennedy KM, Devous MD Sr, et al. Beta-amyloid burden in healthy aging: regional distribution and cognitive consequences. *Neurology* 2012;78:8387–95

17. Sperling RA, Johnson KA, Doraiaiswamy PM, et al. Amyloid deposition detected with florbetapir F 18 (18F-AV-45) is related to lower episodic memory performance in clinically normal older individuals. *Neurobiol Aging* 2013;34:822–31

18. Hedden T, Oh H, Younger AP, et al. Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology* 2013;80:1341–48

19. Lim YY, Ellis KA, Ames D, et al. Abeta amyloid, cognition, and APOE genotype in healthy older adults. *Alzheimers Dement* 2013;9:538–45

20. Fleisher AS, Chen K, Liu X, et al. Apolipoprotein E epsilon4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease. *Neurobiol Aging* 2013;34:1–12

21. Ledesma MD, Medina M, Avila I. The in vitro formation of recombinant tau polymers: effect of phosphorylation and glycation. *Mol Chem Neurropathol* 1996;27:249–58

22. Dubelaar EJ, Verwer RW, Hofman MA, et al. ApoE epsilon4 genotype is accompanied by lower metabolic activity in nucleus basalis of Meynert neurons in Alzheimer patients and controls as indicated by the size of the Golgi apparatus. *J Neuropathol Exp Neurol* 2004;63:159–69

23. Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement* 2011;7:257–62

24. 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;7:280–92

25. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology* 2008;30:58–69

26. Jack CR Jr, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer’s Association criteria for preclinical Alzheimer disease. *Ann Neurol* 2012;71:765–75

27. Knopman DS, Jack CR Jr, Wiste HJ, et al. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology* 2012;78:1576–82

28. Knopman DS, Jack CR Jr., Wiste HJ, et al. Brain injury biomarkers are not dependent on beta-amyloid in normal elderly. *Ann Neurol* 2012 Nov 23. [Epub ahead of print]

29. Petersen RC, Aisen P, Boeve BF, et al. Criteria for mild cognitive impairment due to Alzheimer’s disease in the community. *Ann Neurol* 2013 May 20. [Epub ahead of print]

30. Mosconi L, Andrews RD, Matthews DC. Comparing brain amyloid deposition, glucose metabolism, and atrophy in mild cognitive impairment with and without a family history of dementia. *J Alzheimers Diment* 2013:59:509–24

31. Vemuri P, Lennick TG, Przybelski SA, et al. Effect of lifestyle activities on Alzheimer disease biomarkers and cognition. *Ann Neurol* 2012;72:730–38

32. Kemppainen NM, Aalto S, Karrasch M, et al. Cognitive reserve hypothesis: Pittsburgh compound B and fluorodexoyglucosine positron emission tomography in relation to education in mild Alzheimer’s disease. *Ann Neurol* 2008:63:112–18

33. Mathis CA, Wang Y, Holt DP, et al. Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. *J Med Chem* 2003;46:2740–54

34. Manook A, Yousefi BH, Williweit A, et al. Small-animal PET imaging of amyloid-beta plaques with [11C]PiB and its multi-modal validation in an APP/PS1 mouse model of Alzheimer’s disease. *PLos One* 2012;7:e31130

35. Ikonomovic MD, Kluse WE, Abrahamson EE, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer’s disease. *Brain* 2006;131:1630–45

36. Choi SR, Schneider JA, Bennett DA, et al. Correlation of amyloid PET ligand florbetapir F 18 binding with Abeta aggregation and neuritic plaque deposition in postmortem brain tissue. *Alzheimer Dis Assoc Disord* 2012;26:8–16

37. Lin KJ, Hsu WC, Hsiao IT, et al. Whole-body biodistribution and brain PET imaging with [18F]AV-45, a novel amyloid imaging agent—a pilot study. *Nucl Med Biol* 2010;37:497–508

38. Wong DF, Rosenberg PB, Zhou Y, et al. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18). *J Nucl Med* 2010;51:913–20

39. Poinsel G, Dhilly M, Moustie O, et al. PET imaging with [18F]AV-45 in an APP/PS1–21 murine model of amyloid plaque deposition. *Neurobiol Aging* 2012;33:2561–71

40. Csanéyi Z, Jonhagen ME, Forberg A, et al. Clinical validation of 18F-AZD4694, an amyloid-beta-specific PET radioligand. *J Nucl Med* 2012;53:415–24

41. Rowe CC, Pejoska S, Mulligan RS, et al. Head-to-head comparison of 11C-PiB and 18F-AZD4694 (NAV4694) for beta-amyloid imaging in aging and dementia. *J Nucl Med* 2013;54:880–86

42. Villemagne VL, Mulligan RS, Pejoska S, et al. Comparison of 11C-PiB and 18F-florbetaben for Abeta imaging in aging and Alzheimer’s disease. *Eur J Nucl Med Mol Imaging* 2012;39:983–89

43. Wolk DA, Zhang Z, Boudhar S, et al. Amyloid imaging in Alzheimer’s disease: comparison of florbetapir and Pittsburgh compound-B positron emission tomography. *J Nucl Neurol Surg Psychiatry* 2012;83:923–26

44. Becker GA, Ichise M, Bartelh H, et al. PET quantification of 18F-florbetaben binding to beta-amyloid deposits in human brains. *J Nucl Med* 2013;54:723–31
45. Landau SM, Breault C, Joshi AD, et al. Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J Nucl Med 2013;54:70–77
46. Burack MA, Hartlein J, Flores HP, et al. In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia. Neurology 2010;74:77–84
47. Kantarci K, Yang C, Schneider JA, et al. Antemortem amyloid imaging and beta-amyloid pathology in a case with dementia with Lewy bodies. Neurobiol Aging 2012;33:878–85
48. Fodero-Tavolotti MT, Smith DP, McLean CA, et al. In vitro characterization of Pittsburgh compound-B binding to Lewy bodies. J Neurosci 2007;27:10365–71
49. Ye L, Velasco A, Fraser G, et al. In vitro high affinity alpha-synuclein binding sites for the amyloid imaging agent PIB are not matched by binding to Lewy bodies in postmortem human brain. J Neurochem 2008;105:1428–37
50. Lockhart A, Lamb JR, Osredkar T, et al. PIB is a non-specific imaging marker of amyloid-beta (Abeta) peptide-related cerebral amyloidosis. Brain 2007;130:2607–15
51. Ikonomovic MD, Abrahamson EE, Price JC, et al. Early AD pathology in a C1-PII-negative case: a PIB-amyloid imaging, biochemical, and immunohistochemical study. Acta Neuropathol 2012;123:433–47
52. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011;305:275–83
53. Sojkova J, Driscol I, Iacono D, et al. In vivo fibrillar beta-amyloid detected using [11C]PiB positron emission tomography and neuro-pathologic assessment in older adults. Arch Neurol 2011;68:252–40
54. Kantarci K, Lowe VJ, Boeve BF, et al. Multimodality imaging characteristics of dementia with Lewy bodies. Neurobiol Aging 2012;33:2091–105
55. Villemagne VL, Ong K, Mulligan RS, et al. Amyloid imaging with [18F]florbetaben in Alzheimer disease and other dementias. J Nucl Med 2011;52:1210–17
56. Rabinovici GD, Rosen HJ, Alkalay A, et al. Amyloid PET imaging in patients with mild cognitive impairment: a 2-year follow-up study. Neurology 2011;76:1085–90
57. Schneider JA, Arvanitakis Z, Bang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–204
58. Sonnen JA, Santa Cruz K, Hemmy LS, et al. Ecology of the aging human brain. Arch Neurol 2011;68:1049–56
59. Edson P, Rowe CC, Rinne JO, et al. Amyloid load in Parkinson’s disease dementia and Lewy body dementia measured with [11C]PiB positron emission tomography. J Neurol Neurosurg Psychiatry 2008;79:1331–38
60. Foster ER, Campbell MC, Burack MA, et al. Amyloid imaging of Lewy body-associated disorders. Mov Disord 2010;25:2516–23
61. Gomperts SN, Rentz DM, Moran E, et al. Imaging amyloid deposition in Lewy body diseases. Neurology 2008;71:903–10
62. Maetzler W, Liebelt I, Reimold M, et al. Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. Neurobiol Dis 2009;34:107–12
63. Kantarci K, Ferman TJ, Boeve BF, et al. Focal atrophy on MRI and neuropathologic classification of dementia with Lewy bodies. Neurology 2012;79:553–60
64. O’Brien JT, Colloby S, Fenwick J, et al. Dopaamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. Arch Neurol 2004;61:919–25
65. Villemagne VL, Okamura N, Pejoska S, et al. Differential diagnosis in Alzheimer’s disease and dementia with Lewy bodies via VMAT2 and amyloid imaging. Neurodegener Dis 2012;10:161–65
66. Camus V, Payoux P, Barre L, et al. Using PET with 18F-AV-45 (florbetapir) to quantify brain amyloid load in a clinical environment. Eur J Nucl Med Mol Imaging 2012;39:621–31
67. Frederiksen KS, Haselbalch SG, Hejl AM, et al. Added diagnostic value of [11C]-PiB-PET in memory clinic patients with uncertain diagnosis. Dement Geriatr Cogn Dis Extra 2012;2:610–21
68. Ossenkoppele R, Prins ND, Pijnenburg YA, et al. Impact of molecular imaging on the diagnostic process in a memory clinic. Alzheimers Dement 2013;9:411–21
69. Frisoni GB, Bocchetta M, Chetelat G, et al. Imaging markers for Alzheimer disease: which vs how. Neurology 2013;81:487–500
70. Mitka M. PET imaging for Alzheimer disease: are its benefits worth the cost? JAMA 2013;309:1099–100
71. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade. Lancet Neurol 2010;9:119–28
72. 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;12:207–16
73. Jack CR Jr, Wiste HJ, Lesnick TG, et al. Brain beta-amyloid load approaches a plateau. Neurology 2013;80:890–96
74. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer’s disease: a prospective cohort study. Lancet Neurol 2013;12:557–67
75. Kadir A, Almkvist O, Forsberg A, et al. Dynamic changes in PET amyloid and FDG imaging at different stages of Alzheimer’s disease. Neurobiol Aging 2012;33:198.e1–14
76. Koivunen J, Scheinin N, Virta JR, et al. Amyloid PET imaging in patients with mild cognitive impairment: a 2-year follow-up study. Neurology 2011;76:1085–90
77. Ossenkoppele R, Tolboom N, Foster-Dingley JC, et al. Longitudinal imaging of Alzheimer pathology using [11C]PiB, [18F]FDDNP and [18F]FDG PET. Eur J Nucl Mol Imaging 2012;39:990–1000
78. Sojkova J, Zhou Y, An Y, et al. Longitudinal patterns of beta-amyloid deposition in nondeemented older adults. Arch Neurol 2011;68:644–49
79. Villemagne VL, Pike KE, Chetelat G, et al. Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. Ann Neurol 2011;69:181–92
80. Villain N, Chetelat G, Grassiot B, et al. Regional dynamics of amyloid-beta deposition in elderly, mild cognitive impairment and Alzheimer’s disease: a voxelwise PiB-PET longitudinal study. Brain 2012;135:2126–39
81. Jack CR Jr, Lowe VJ, Weigand SD, et al. Serial PiB and MRI in normal, mild cognitive impairment and Alzheimer’s disease: implications for sequence of pathological events in Alzheimer’s disease. Brain 2009;132:1555–65
82. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer’s disease. N Engl J Med 2012;367:795–804
83. Fleisher AS, Chen K, Quirao YT, et al. Florbetapir PET analysis of amyloid-beta deposition in the presenilin 1 E280A autosomal dominant Alzheimer’s disease kindred: a cross-sectional study. Lancet Neurol 2012;11:1057–65
84. Sperling RA, Jack CR Jr, Aisen PS. Testing the right target and right drug at the right stage. Sci Transl Med 2011;3:111cm33
85. Bartel H, Luthardt J, Becker G, et al. Individualized quantification of brain beta-amyloid burden: results of a proof of mechanism phase 0 florbetaben PET trial in patients with Alzheimer’s disease and healthy controls. Eur J Nucl Mol Imaging 2011;38:1702–14
86. 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 2a controlled, ascending-dose study. Lancet Neurol 2010;9:363–72
87. Small GW, Siddarth P, Kepe V, et al. Prediction of cognitive decline by positron emission tomography of brain amyloid and tau. Arch Neurol 2012;69:215–22
88. Small GW, Kepe V, Ercoli LM, et al. PET of brain amyloid and tau in mild cognitive impairment. N Engl J Med 2006;355:2652–63
89. Okamura N, Furumoto S, Harada R, et al. Novel 18F-labeled arylquinoline derivatives for noninvasive imaging of tau pathology in Alzheimer disease. J Nucl Med 2013;54:1420–27
90. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94