Bibliographic Cite	PMID Link	Literature Type	Level of Evidence	Purpose	Population	Intervention and Outcome Measures	Results/ Recommendations	Study Limitiations
Allali G, Garibotto V, Mainta IC, Nicastro N, Assal F. Dopaminergic imaging separates normal pressure hydrocephalus from its mimics. J Neurol. 2018; 265(10):2434-2441.	30155736	Single-center, retrospective, consecutive, multi-reader	low level of evidence	To compare [123I]FP-CIT SPECT imaging-visual rating and semiquantitative values-between iNPH and iNPH mimics.	56 patients with a suspicion of iNPH (76.5 ± 6.1 years; 23.2% women) based on gait and/or cognitive impairments with ventricular enlargement at brain imaging (CT or MRI) defined by an Evans ratio > 0.30. Inclusion criteria for this analysis were (1) completion of [123I]FP-CIT SPECT with a maximum interval of 3 months since diagnosis and (2) a comprehensive neurological assessment concluding to the diagnosis of iNPH versus iNPH mimics. Exclusion criteria were presence of an acute medical illness in the past 3 months and a diagnosis of secondary NPH.	26 patients fulfilled the iNPH diagnostic criteria and the remaining 30 were classified as iNPH mimics. Patients were visually categorized as having normal or abnormal [123I]FP-CIT SPECT; and for the quantification of the [123I]FP-CIT SPECT imaging, authors calculated striatal binding ratios (SBR) using BRASS™ automated brain analysis while applying locally established reference limits (adjusted for age). Logistic regressions were used to assess the association between [123I]FP-CIT SPECT and diagnostic groups.	A normal SBR [123I]FP-CIT SPECT was present in 69.2% of iNPH and 37.9% of mimics (p value = .020), while visual rating did not differ between the two groups. Normal SBR [123I]FP-CIT SPECT values were associated with the diagnosis of iNPH, even after adjusting for white matter changes and comorbidities (adjusted odds ratio: 4.17; 95% CI 1.26–13.80). The authors conclude that semi-quantitative [123I]FP-CIT SPECT evaluation, but not visual assessment, discriminates iNPH patients from their mimics. [123I]FP-CIT SPECT represents an interesting neuroimaging biomarker to improve the selection of patients with iNPH for invasive shunt surgery.	This study is not without limitations due to the absence of a pathological confirmation and its retrospective design that prevents the inclusion of a systematic post-shunt assessment and cannot, therefore, exclude a selection bias. The absence of pathological confirmation for subjects reflects the daily clinical practice. Therefore, these results can merely apply to clinical phenotypes and further investigations are required to assess whether [123I]FP-CIT SPECT is correlated with neuropathology-confirmed cases.
Barrou Z, Boddaert J, Faucounau V, et al. Utility of 123I-FP-CIT SPECT for dementia diagnoses and therapeutic strategies in elderly patients. Journal of Nutrition, Health & Aging. 2014;18(1):50-3.	24402389	Evaluation Studies	low level of evidence	To evaluate the influence of single photon emission computed tomography (SPECT) of the dopamine transporter (123I-FP-CIT) on diagnosis and treatment strategies in elderly patients with mild dementia.	Consecutive ambulatory patients who had 123I-FP-CIT SPECT for a suspicion of DLB. Clinical diagnoses before SPECT were compared with imaging results.46 patients were included. Pre imaging clinical hypotheses were probable DLB in 14, possible DLB in 21 and alternate diagnoses in 11.	46 patients were included. Pre imaging clinical hypotheses were probable DLB in 14, possible DLB in 21 and alternate diagnoses in 11. Rates of abnormal imaging in these groups were respectively 71%, 43% and 18%. Overall, diagnoses were revised in 37% of the cases. Four patients with probable DLB had normal imaging. Their number of core criteria did not differ from the remainder (2.75 +/- 0.5 vs. 2.1 +/- 0.6), but hallucinations in 2 patients were not well formed and detailed as usual in DLB. Among 38 patients free of antipsychotics, rates of abnormal scans were 36% in patients with questionable parkinsonism, 57% in definite parkinsonism, 67% in patients with no parkinsonism. Among 9 patients on Levodopa, 6 had normal scans and Levodopa was stopped.	The authors show a significant impact of 123I-FP-CIT SPECT on diagnoses, even in cases of definite parkinsonism or probable DLB. In the latter, scarcity of hallucinations, especially if there are not well formed and detailed, should prompt 123I-FP-CIT SPECT.	Readers were not blinded or no comment was made about the blinding of the readers; Single reader or no inter-reader reliability was calculated.
Benedetto N, Gambacciani C, Aquila F, et al. A new quantitative method to assess disproportionately enlarged subarachnoid space (DESH) in patients with possible idiopathic normal pressure hydrocephalus: The SILVER index. Clinical Neurology & Neurosurgery. 2017;158:27-32.	28448824	Retrospective study	low level of evidence	To describe a new quantitative method to assess DESH on CT scans and to evaluate its prognostic value.	A multiplanar reconstruction software was used to retrospectively evaluate prospectively collected radiological data (CT scans) of 26 controls and 29 consecutive patients that underwent VP shunt placement for possible iNPH. The ratio between the areas of the sylvian fissure and the subarachnoid space at the vertex was calculated (SILVER index). The diagnostic accuracy of the SILVER index and the estimate of the best cut-point were assessed using ROC analysis.	The mean value of the SILVER index was 11.52+/-14.27 in the study group and 1.68+/-0.98 in the control group (p-value<0.0001). The area under the ROC curve for the SILVER index was 0.903 (95% CI 0.813-0.994). A cut-off value for the SILVER index of 3.75 was extrapolated with a sensitivity and specificity of 0.828 and 0.962 respectively.	The SILVER index is a reliable tool to easily quantify DESH on CT scans of patients with suspected iNPH. Its high sensitivity and specificity should encourage further investigations in order to confirm its clinical utility.	Readers were not blinded or no comment was made about the blinding of the readers; Single reader or no inter-reader reliability was calculated.
Bensaidane MR, Beauregard JM, Poulin S, et al. Clinical Utility of Amyloid PET Imaging in the Differential Diagnosis of Atypical Dementias and Its Impact on Caregivers. Journal of Alzheimer's Disease. 2016;52(4):1251-62.	27104896	Research Support, Non-U.S. Gov't	moderate level of evidence	To investigate the clinical utility of amyloid PET in the differential diagnosis of atypical dementia cases and its impact on caregivers.	Using the amyloid tracer 18F-NAV4694, the authors prospectively scanned 28 patients (mean age 59.3 y, s.d. 5.8; mean MMSE 21.4, s.d. 6.0) with an atypical dementia syndrome. Following a comprehensive diagnostic workup (i.e., history taking, neurological examination, blood tests, neuropsychological evaluation, MRI, and FDG-PET), no certain diagnosis could be arrived at. Amyloid PET was then conducted and classified as positive or negative. Attending physicians were asked to evaluate whether this result led to a change in diagnosis or altered management. They also reported their degree of confidence in the diagnosis. Caregivers were met after disclosure of amyloid PET results and completed a questionnaire/interview to assess the impact of the scan.	The authors' cohort was evenly divided between positive (14/28) and negative (14/28) 18F-NAV4694 cases. Amyloid PET resulted in a diagnostic change in 9/28 cases (32.1%: 17.8% changed from AD to non-AD, 14.3% from non-AD to AD). There was a 44% increase in diagnostic confidence. Altered management occurred in 71.4% (20/28) of cases. Knowledge of amyloid status improved caregivers' outcomes in all domains (anxiety, depression, disease perception, future anticipation, and quality of life). This study suggests a useful additive role for amyloid PET in atypical cases with an unclear diagnosis beyond the extensive workup of a tertiary memory clinic.	Amyloid PET increased diagnostic confidence and led to clinically significant alterations in management. The information gained from that test was well received by caregivers and encouraged spending quality time with their loved ones.	Reference standard was inadequate; The authors used an internally-developed survey/questionnaire that had not been previously validated externally; Small sample size.
Brix MK, Westman E, Simmons A, et al. The Evans' Index revisited: New cut-off levels for use in radiological assessment of ventricular enlargement in the elderly. European Journal of Radiology. 2017;95:28-32.	28987681	Retrospective study	moderate level of evidence	To propose new age and sex specific cut-off values for ventricular enlargement in the elderly population.	534 participants (53% women) aged 65-84 years; 226 patients with Alzheimer's disease (AD), and 308 healthy elderly controls (CTR) from the AddNeuroMed and ADNI studies were included.	The cut-off for pathological ventricular enlargement was estimated from healthy elderly categorized into age groups of 5 years range and defined as EI 97,5 percentile (mean+2SD). Cut-off values were tested on patients with Alzheimer's disease and a small sample of patients with probable idiopathic normal pressure hydrocephalus (iNPH) to assess the sensitivity. The range of the EI in healthy elderly is wide and 29% of the CTR had an EI of 0.3 or greater. The EI increases with age in both CTR and AD, and the overall EI for women were lower than for men (p<0.001). New EI cut off values for male/female: 65-69 years 0.34/0.32, 70-74 years 0.36/0.33, 75-79 years 0.37/0.34 and 80-84 years 0.37/0.36. When applying the proposed cut-offs for EI in men and women aged 65-84, they differentiated between iNPH and CTR with a sensitivity of 80% and for different age and sex categories of AD and CTR with a sensitivity and specificity of 0-27% and 91-98%, respectively.	The range of the EI measurements in healthy elderly is wide, and a cut-off value of 0.3 cannot be used to differentiate between normal and enlarged ventricles in individual cases. The proposed EI thresholds from the present study show good sensitivity for the iNPH diagnosis.	Non-consecutive recruitment.
Cagnin A, Simioni M, Tagliapietra M, et al. A Simplified Callosal Angle Measure Best Differentiates Idiopathic-Normal Pressure Hydrocephalus from Neurodegenerative Dementia. Journal of Alzheimer's Disease. 2015;46(4):1033-8.	26402630	Cohort study	low level of evidence	To study the accuracy of a simplified callosal angle measure in differentiating iNPH from DLB and AD using conventional brain MRI.	76 patients (24 iNPH, 30 DLB, 22 AD) and 40 healthy controls served as discovering cohort. 41 patients (21 iNPH and 20 DLB/AD) were used as independent validation cohort. A set of other conventional MRI markers of iNPH was also evaluated.	iNPH showed a significantly decreased mean callosal angle value compared to both disease groups and controls (iNPH = 109+/-9; DLB = 136.9+/-8.2; AD = 135.4+/-11.3; Controls = 138.5+/-5.2; p < 0.00001). Using a cut off angle of 123, derived by the mean -3SD of the control group, an accuracy of 96% (sensitivity 100% , specificity 95.4%) was obtained. By ROC analysis, the area under the curve was 0.99 (95% CI: 0.97-1). The measure was consistent (intra-rater: r = 0.94) and reproducible (inter-rater: r = 0.89). In the validation cohort, this cut off angle value discriminated iNPH from DLB/AD with 97.5% accuracy. None of the conventional MRI signs reached the same accuracy.	This simplified callosal angle measure represents an accurate, reproducible, and easy marker of iNPH.	Reference standard was inadequate; The inclusion of multiple dementia subtypes based on clinical criteria may confound results.

Canu E, Agosta F, Mandic-Stojmenovic G, et al. Multiparametric MRI to distinguish early onset Alzheimer's disease and behavioural variant of frontotemporal dementia. NeuroImage Clinical. 2017;15:428-38.	28616383	Prospective study	low level of evidence	To explore whether an approach combining structural [cortical thickness and white matter (WM) microstructure] and resting state functional MRI can aid differentiation between 62 early onset Alzheimer's disease (EOAD) and 27 behavioural variant of frontotemporal dementia (bvFTD) patients.	62 early onset Alzheimer's disease (EOAD) and 27 behavioural variant of frontotemporal dementia (bvFTD) patients.	Random forest and receiver operator characteristic curve analyses assessed the ability of MRI in classifying the two clinical syndromes. All patients showed a distributed pattern of brain alterations relative to controls. Compared to bvFTD, EOAD patients showed bilateral inferior parietal cortical thinning and decreased default mode network functional connectivity. Compared to EOAD, bvFTD patients showed bilateral orbitofrontal and temporal cortical thinning, and WM damage of the corpus callosum, bilateral uncinate fasciculus, and left superior longitudinal fasciculus. Random forest analysis revealed that left inferior parietal cortical thickness (accuracy 0.78, specificity 0.76, sensitivity 0.83) and WM integrity of the right uncinate fasciculus (accuracy 0.81, specificity 0.96, sensitivity 0.43) were the best predictors of clinical diagnosis. The combination of cortical thickness and DT MRI measures was able to distinguish patients with EOAD and bvFTD with accuracy 0.82, specificity 0.76, and sensitivity 0.96. The diagnostic ability of MRI models was confirmed in a subsample of patients with biomarker-based clinical diagnosis.	Multiparametric MRI is useful to identify brain alterations which are specific to EOAD and bvFTD. A severe cortical involvement is suggestive of EOAD, while a prominent WM damage is indicative of bvFTD.	Readers were not blinded or no comment was made about the blinding of the readers; Single reader or no inter-reader reliability was calculated; small sample.
Craven CL, Toma AK, Mostafa T, et al. The predictive value of DESH for shunt responsiveness in idiopathic normal pressure hydrocephalus. Journal of Clinical Neuroscience. 2016;34:294-8.	27692614	Retrospective study	low level of evidence	To calculate the negative predictive value of the DESH sign.	A single centre study of probable INPH patients, who underwent ventriculoperitoneal (VP) shunt insertion. Shunt responsive INPH patients were identified as those having improvement in their walking speed, neuropsychological assessment and continence one year post operatively. Preoperative images were reviewed for DESH sign. Negative and Positive Predictive Values (NPV and PPV) of DESH sign were determined post analysis. A total of 103 probable INPH patients were included (31 were DESH positive (30%) and 72 were DESH negative (70%)).	A total of 78 patients showed measurable improvement one year post shunt insertion (76%); 24 (31%) of these patients were DESH positive and 54 (69%) were DESH negative (p=<0.001). Therefore, the DESH sign had an estimated PPV of 77% and NPV of 25%.	DESH sign demonstrates a low negative predictive value. The authors conclude that DESH negative patients should still undergo prognostic tests for iNPH, such as an extended lumbar drainage protocol, and should not be excluded from shunt insertion.	Single reader or no inter-reader reliability was calculated.
de Wilde A, van der Flier WM, Pelkmans W, Bouwman F, Verwer J, Groot C, van Buchem MM, Zwan M, Ossenkoppele R, Yagub M, Kunneman M, Smets EM, Barkhof F, Lammertsma AA, Stephens A, van Lier E, Biessels GJ, van Berckel BN, Scheltens P. Association of amyloid positron emission tomography with changes in diagnosis and patient treatment in an unselected memory clinic cohort: The ABIDE Project. JAMA Neurol. 2018; 75(9):1062-1070.	29889941	Single-center, prospective, consecutive, multi-reader	moderate level of evidence	To evaluate the association of amyloid PET with changes in diagnosis, diagnostic confidence, treatment, and patients' experiences in an unselected memory clinic cohort	Patients who were visiting the memory clinic of the VU University Medical Center (VUMC) between January 2015 and December 2016. Additionally, the authors included patients with MCI from the University Medical Center Utrecht (UMCU) memory clinic. A total of 866 patients at the VUMC to participate, of whom 476 were included, 32 were excluded, and 358 did not participate. The total number available for analysis was 507 (VUMC,476[93.9%];UMCU, 31 [6.1%]).Compared with the nonparticipants, participating patients tended to be older(mean[SD] age,65 [8] vs 62 [9] years;P = .09), more often male (306 [60%] vs 195 [50%]; P < .01), have a higher Mini-Mental State Examination score (mean [SD], 25 [3] vs 23 [6]; P < .01), and a positive family history of dementia (235 [46%]vs 152 [39%];P < .01).	For each patient, neurologists determined a preamyloid and postamyloid PET diagnosis that existed of both a clinical syndrome (dementia, mild cognitive impairment, or subjective cognitive decline) and a suspected etiology (Alzheimer disease [AD] or non-AD), with a confidence level ranging from 0%to 100%. In addition, the neurologist determined patient treatment interms of ancillary investigations, medication, and care.Each patient received a clinical follow-up 1 year after being scanned. Primary outcome measures were post-PET changes in diagnosis, diagnostic confidence, and patient treatment.	Of the 507 patients (mean [SD] age, 65 (8) years; 201 women [39%]; mean [SD] Mini-Mental State Examination score, 25 [4]), 164 (32%) had AD dementia, 70 (14%) non-AD dementia, 114 (23%) mild cognitive impairment, and 159 (31%) subjective cognitive decline. Amyloid PET results were positive for 242 patients (48%). The suspected etiology changed for 125 patients (25%) after undergoing amyloid PET, more often due to a negative (82 of 265 [31%]) than a positive (43 of 242 [18%]) PET result (P < .01). Post-PET changes in suspected etiology occurred more frequently in patients older (>65 years) than younger (<65 years) than the typical age at onset of 65 years (74 of 257 [29%] vs 51 of 250 [20%]; P < .05). Mean diagnostic confidence (SD) increased from 80 (13) to 89 (13%) (P < .001). In 123 patients (24%), there was a change in patient treatment post-PET, mostly related to additional investigations and therapy. The authors conclude that this prospective diagnostic study provides a bridge between validating amyloid PET in a research setting and implementaing this diagnostic tool in daily clinical practice. Both amyloid-positive and amyloid-negative results had substantial associations with changes in diagnosis and treatment, both in patients with and without dementia.	First, the main outcome measure was change in diagnosis. Because postmortem verification was not available, this outcome measure reflects, at least in part, the clinicians' beliefs. Second, being a tertiary referral center, the routine diagnostic workup is quite extensive. This may have led to an underestimation of the association of amyloid PET. Third, most patients were included in a tertiary referral center, with a high proportion of young patients with often complex clinical presentations. This may hamper the translation to primary care and local memory clinics. Fourth, the study setup deviates from regular clinical practice in several important ways, as authors offered amyloid PET to all patients rather than diagnostically uncertain cases, the primary neurologist may or may not have seen the patient, results were not always disclosed to patients, and patients had no financial liability. Finally, patients were included in this study based on self-selection instead of a randomization process.
Ding Y, Sohn JH, Kawczynski MG, et al. A deep learning model to predict a diagnosis of Alzheimer disease by using 18F-FDG PET of the brain. Radiology. 2019; 290(2):456-464.	30398430	Multi-center, retrospective, non-consecutive, multi-reader	moderate level of evidence	To develop and validate a deep learning algorithm that predicts the final diagnosis of Alzheimer disease (AD), mild cognitive impairment, or neither at fluorine 18 (18F) fluorodeoxyglucose (FDG) PET of the brain and compare its performance to that of radiologic readers.	Patients from both the Alzheimer's Disease Neuroimaging Initiative (ADNI) and a retrospective independent test set were included. The ADNI set included 2109 imaging studies from 1002 patients. The average age of the patients was 76 years (55–93 yrs) for men and 75 years (55–96 yrs) for women (P < .001), with an average age of 77 years (56–92 yrs) for men and 75 years (55–93 yrs) for women in the AD group (P = .04), 76 years (55–93 yrs) for men and 74 years (57–91 yrs) for women in the MCI group (P = .01), and 76 years (60–90 yrs) for men and 75 years (60–96 yrs) for women in the non-AD/MCI group (P = .14). The overall percentage of men was 54% (547 of 1002) by patient and 58% (1225 of 2109) by imaging study. The average follow-up period of the patients was 54 months by patient and 62 months by imaging study. The independent test set was composed of 40 patients, with seven clinically diagnosed as having AD, seven having MCI, and 26 having non-AD/MCI at the end of the follow-up period. The average age of the 40 test patients was 66 years (48–84 yrs) for men and 71 years (41–84 yrs) for women, with an average age of 69 years (56–79 yrs) for men and 73 years (73–73 yrs) for women in the AD group, 63 years (48–83 yrs) for men and 68 years (68–68 yrs) for women in the MCI group, and 66 years (55–84 yrs) for men and 71 years (41–84 yrs) for women in the non-AD/MCI group. The overall percentage of men was 58% (23 of 40), while the percentage in the AD, MCI, and non-AD/ MCI group was 86%, 86%, and 42%, respectively. The average follow-up period of the patients was 76 months, with an average of 82 months in the AD group, 75 months in the MCI group, and 74 months in the non-AD/MCI group.	All images were collected and final clinical diagnosis at follow-up was recorded. Convolutional neural network of InceptionV3 architecture was trained on 90% of ADNI data set and tested on the remaining 10%, as well as the independent test set, with performance compared to radiologic readers. Model was analyzed with sensitivity, specificity, receiver operating characteristic (ROC), saliency map, and t-distributed stochastic neighbor embedding. To obtain reader performance on the independent test set, three board-certified nuclear medicine physicians with 36, 14, and 5 years of experience, respectively, performed independent interpretations of the 40 18F-FDG PET imaging studies from the independent test set. Interpretations consisted of two components: qualitative interpretation of the PET emission images in axial, sagittal, and coronal planes, followed by a semiquantitative regional metabolic analysis using a commercially available clinical neuro-analysis software package.	The algorithm achieved area under the ROC curve of 0.98 (95% confidence interval: 0.94, 1.00) when evaluated on predicting the final clinical diagnosis of AD in the independent test set (82% specificity at 100% sensitivity), an average of 75.8 months prior to the final diagnosis, which in ROC space outperformed reader performance (57% sensitivity, 91% specificity; P , .05). Saliency map demonstrated attention to known areas of interest but with focus on the entire brain. The authors conclude that by using fluorine 18 fluorodeoxyglucose PET of the brain, a deep learning algorithm developed for early prediction of Alzheimer disease achieved 82% specificity at 100% sensitivity, an average of 75.8 months prior to the final diagnosis.	First, independent test data were relatively small (n = 40) and were not collected as part of a clinical trial. This was a highly selected cohort in that all patients must have been referred to the memory clinic and neurologist must have decided that a PET study of the brain would be useful in clinical management. Second, the deep learning algorithm's robustness is inherently limited by the clinical distribution of the training set from ADNI. This training set from ADNI did not include non-AD neurodegenerative cases, limiting the utility of the algorithm in such patient population. Third, the deep learning algorithm did not yield a human interpretable imaging biomarker despite visualization with saliency map, which highlights the inherent black-box limitation of deep learning algorithms. Fourth, MCI and non-AD/MCI were inherently unstable diagnoses in that their accuracy is dependent on the length of follow-up.

Donaghy PC, Firbank MJ, Thomas AJ, Lloyd J, Petrides G, Barnett N, Olsen K, O'Brien JT. Clinical and imaging correlates of amyloid deposition in dementia with Lewy bodies. Mov Disord. 2018; 33(7):1130-1138.	29672930	Single-center, prospective, non-consecutive, multi-reader	low level of evidence	To investigate the relationship between amyloid deposition and clinical profile, gray matter volume, and brain perfusion in dementia with Lewy bodies.	Patients included those with dementia with Lewy bodies (n = 37), Alzheimer's disease (n = 20), and controls (n = 20). Participants were recruited prospectively between June 2013 and February 2016 from secondary care services in the North of England. Control participants were recruited through a research case register or were partners of participants. All participants were 60 years old. Dementia patients had a diagnosis of probable DLB or probable AD confirmed by 2 clinicians based on contemporaneous diagnostic criteria, with an MMSE 12. Participants were excluded if they had a major concurrent psychiatric illness, severe physical illness, contraindications to PET-CT imaging, a history of other significant neurological illness including stroke, previous experimental treatment with an amyloid-targeting agent, or current treatment with any other investigational agent.	All patients underwent a thorough clinical assessment, 3T MRI, and early- and late-phase 18F-Florbetapir PET-CT to assess cortical perfusion and amyloid deposition, respectively. Amyloid scans were visually categorized as positive or negative. Image analysis was carried out using statistical parametric mapping (SPM) 8. Amyloid PET images were reviewed by 5 raters, all of whom had completed certified training in amyloid image reading. Raters were blinded to all clinical data.	There were no significant differences between amyloid-positive and amyloid-negative dementia with Lewy bodies cases in age (P = .78), overall cognitive impairment (P = .83), level of functional impairment (P = .80), or any other clinical or cognitive scale. There were also no significant differences in hippocampal or gray matter volumes. However, amyloid-positive dementia with Lewy bodies cases had lower medial temporal lobe perfusion (P = .03) than amyloid-negative cases, although a combination of medial temporal lobe perfusion, hippocampal volume, and cognitive measures was unable to accurately predict amyloid status in dementia with Lewy bodies. The authors conclude that amyloid deposition was not associated with differences in clinical or neuropsychological profiles in dementia with Lewy bodies, but was associated with imaging evidence of medial temporal lobe dysfunction. The presence of amyloid in dementia with Lewy bodies cannot be identified on the basis of clinical and other imaging features and will require direct assessment via PET imaging or CSF.	A total of 6 DLB patients and 1 AD patient were unable to have MRI scans as a result of metal implants. Some patients did not have complete data, principally as result of an inability to complete 1 or more parts of the cognitive assessment. The authors could not exclude the possibility that the amyloid positive control cases reflect preclinical AD. Excluding these cases would increase the difference between DLB and controls, but the findings would be less generalizable to the general population. Selection bias is an important factor to consider when interpreting these results.
Fayed N, Modrego PJ, Garcia-Marti G, et al. Magnetic resonance spectroscopy and brain volumetry in mild cognitive impairment. A prospective study. Magnetic Resonance Imaging. 2017;38:27-32.	27964994	Prospective studies	moderate level of evidence	To assess the accuracy of magnetic resonance spectroscopy (1H-MRS) and brain volumetry in mild cognitive impairment (MCI) to predict conversion to probable Alzheimer's disease (AD).	Forty-eight patients fulfilling the criteria of amnestic MCI who underwent a conventional magnetic resonance imaging (MRI) followed by MRS, and T1-3D on 1.5 Tesla MR unit. At baseline the patients underwent neuropsychological examination. 1H-MRS of the brain was carried out by exploring the left medial occipital lobe and ventral posterior cingulated cortex (vPCC) using the LCModel software. A high resolution T1-3D sequence was acquired to carry out the volumetric measurement. A cortical and subcortical parcellation strategy was used to obtain the volumes of each area within the brain. The patients were followed up to detect conversion to probable AD.	After a 3-year follow-up, 15 (31.2%) patients converted to AD. The myo-inositol in the occipital cortex and glutamate+glutamine (Glx) in the posterior cingulate cortex predicted conversion to probable AD at 46.1% sensitivity and 90.6% specificity. The positive predictive value was 66.7%, and the negative predictive value was 80.6%, with an overall cross-validated classification accuracy of 77.8%. The volume of the third ventricle, the total white matter and entorhinal cortex predict conversion to probable AD at 46.7% sensitivity and 90.9% specificity. The positive predictive value was 70%, and the negative predictive value was 78.9%, with an overall cross-validated classification accuracy of 77.1%. Combining volumetric measures in addition to the MRS measures the prediction to probable AD has a 38.5% sensitivity and 87.5% specificity, with a positive predictive value of 55.6%, a negative predictive value of 77.8% and an overall accuracy of 73.3%.	Either MRS or brain volumetric measures are markers separately of cognitive decline and may serve as a noninvasive tool to monitor cognitive changes and progression to dementia in patients with amnestic MCI, but the results do not support the routine use in the clinical settings.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled; Non-consecutive recruitment; Single reader or no inter-reader reliability was calculated.
Fischbach-Boulanger C, Fitsiori A, Noblet V, Baloglu S, Oesterle H, Draghici S, Phillippi N, Duron E, Hanon O, Dietemann JL, Blanc F, Kremer S. T1- or T2-weighted magnetic resonance imaging: What is the best choice to evaluate atrophy of the hippocampus? Eur J Neurol. 2018; 25(5):775-781.	29442416	Multi-center, prospective, non-consecutive, multi-reader	moderate level of evidence	To evaluate which sequence of T1-weighted (T1WI) and T2-weighted (T2WI) imaging allowed the best visual evaluation of hippocampal atrophy.	150 subjects (50 with AD and 100 with MCI) were selected from two centers. Each subject included in the study was diagnosed and followed up in their own center. The MCI group included 66 women and 34 men (aged 79.06 +/- 5.50 years) and the AD group included 34 women and 16 men (aged 80.87 +/- 6.02 years). Inclusion criteria were both men and women aged 70 years or older. A sufficient educational level and adequate aptitude in French were required to avoid bias on the neuropsychological tests. Exclusion criteria included psychological diseases and other neurological and medical conditions that could affect vision and hearing, making the tests impossible to complete. Subjects with contraindications to MRI (cardiac pacemaker, neuromodulation systems, audio prosthesis, ocular metallic foreign bodies, etc.) were also excluded.	Each subject underwent a full clinical examination and several neuropsychological tests including the MMSE and two anterograde memory tests, i.e. the Free and Cued Selective Reminding Test (FCSRT) and Delayed Matching to Sample 48 Items (DMS48). Visual qualitative ratings of the patients were made independently by four operators according to the medial temporal lobe atrophy score based either on T1WI or T2WI. These two evaluations were compared in terms of interobserver reproducibility, concordance with a quantitative volumetric measure, discrimination power between AD and MCI groups, and correlation with several neuropsychological tests.	The medial temporal lobe atrophy score evaluated on either T1WI or T2WI exhibited similar interobserver variability and accordance with quantitative volumetric evaluation. However, the visual evaluation on T2WI seemed to provide better discrimination power between AD and MCI groups for both left (T1WI, P = 0.0001; T2WI, P = 0.00007072) and right (T1WI, P = 0.008; T2WI, P = 0.001) hippocampus, and a higher overall correlation with neuropsychological tests. The authors conclude that the present study suggests that T2WI provides a more adequate visual rating of hippocampal atrophy.	First, a visual estimation is qualitative and thus not highly reproducible; despite efforts to eliminate this bias by using a third person to pre-process the data and to make the multiplanar reconstruction in the same axis for every reader, there is only fair agreement in the results of the four operators. In addition, for the comparison between qualitative and quantitative methods, authors could not perform quantitative volumetric measurement on the T2WI sequences, as most of the software developed for brain volumetric studies, including Free-Surfer, was developed for T1WI sequences, which is considered to be the gold standard for global and regional brain volumetric studies.
Garcia-Armengol R, Domenech S, Botella-Campos C, et al. Comparison of elevated intracranial pressure pulse amplitude and disproportionately enlarged subarachnoid space (DESH) for prediction of surgical results in suspected idiopathic normal pressure hydrocephalus. Acta Neurochirurgica. 2016;158(11):2207-13.	27349896	Comparative Study	moderate level of evidence	To compare the prognostic value of pulse amplitude on intracranial pressure (ICP) monitoring and disproportionately enlarged subarachnoid space hydrocephalus (DESH) on magnetic resonance imaging (MRI) for predicting surgical benefit after shunt placement in idiopathic normal pressure hydrocephalus (iNPH).	Patients with suspected iNPH were prospectively recruited from a single centre. All patients received preoperative MRI and ICP monitoring. Patients were classified as shunt responders if they had an improvement of one point or more on the NPH score at 1 year post-surgery. The sensitivity, specificity, Youden index, and positive and negative predictive values of the two diagnostic methods were calculated. Sixty-four of 89 patients clinically improved at 1 year post-surgery and were classed as shunt responders.	Positive DESH findings had a sensitivity of 79.4 % and specificity of 80.8 % for predicting shunt responders. Fifty-five of 89 patients had positive DESH findings: 50 of these responded to VP shunt, giving a positive and negative predictive value of 90.9 % and 61.8 %, respectively. Fifty-seven of 89 patients had high ICP pulse amplitude. High ICP pulse amplitude had a sensitivity of 84.4 %, specificity of 88 %, positive predictive value of 94.7 % and negative predictive value of 61.8 % for predicting shunt responders.	Both positive DESH findings and high ICP pulse amplitude support the diagnosis of iNPH and provide additional diagnostic value for predicting shunt-responsive patients; however, high ICP amplitude was more accurate than positive DESH findings, although it is an invasive test.	Non-consecutive recruitment; Single reader or no inter-reader reliability was calculated.
Grill JD, Cox CG, Kremen S, et al. Patient and caregiver reactions to clinical amyloid imaging. Alzheimer's & Dementia. 2017;13(8):924-32.	28174068	Research study	low level of evidence	To examine how amyloid imaging affects the diagnostic experience of patients and families.	The authors interviewed members of 26 patient-caregiver dyads with whom a neurologist discussed the option of amyloid positron emission tomography.	Most participants who chose to undergo amyloid imaging would choose to do so again. Regardless of the scan outcome, patients and caregivers commonly expressed relief on learning the scan results. Some participants expressed expectations that were beyond scan capabilities.	Amyloid imaging may provide information that patients and their families find useful. Clinicians must set correct expectations and ensure that families understand the limitations of amyloid imaging.	High percentage (> 25%) of people who dropped out of the study; Of 26 patient-caregiver dyads, only a handful of dyads had both members complete the survey.
Inui Y, Ito K, Kato T, et al. Longer-Term Investigation of the Value of 18F-FDG-PET and Magnetic Resonance Imaging for Predicting the Conversion of Mild Cognitive Impairment to Alzheimer's Disease: A Multicenter Study. Journal of Alzheimer's Disease. 2017;60(3):877-87.	28922157	Multicenter Study	low level of evidence	To evaluate longer-term prediction of MCI to AD conversion using 18F-FDG-PET and MRI in a multicenter study.	One-hundred and fourteen patients with MCI were followed for 5 years. They underwent clinical and neuropsychological examinations, 18F-FDG-PET, and MRI at baseline. PET images were visually classified into predefined dementia patterns. PET scores were calculated as a semi quantitative index. For structural MRI, z-scores in medial temporal area were calculated by automated volume-based morphometry (VBM).	Overall, 72% patients with amnestic MCI progressed to AD during the 5-year follow-up. The diagnostic accuracy of PET scores over 5 years was 60% with 53% sensitivity and 84% specificity. Visual interpretation of PET images predicted conversion to AD with an overall 82% diagnostic accuracy, 94% sensitivity, and 53% specificity. The accuracy of VBM analysis presented little fluctuation through 5 years and it was highest (73%) at the 5-year follow-up, with 79% sensitivity and 63% specificity. The best performance (87.9% diagnostic accuracy, 89.8% sensitivity, and 82.4% specificity) was with a combination identified using multivariate logistic regression analysis that included PET visual interpretation, educational level, and neuropsychological tests as predictors.	18F-FDG-PET visual assessment showed high performance for predicting conversion to AD from MCI, particularly in combination with neuropsychological tests. PET scores showed high diagnostic specificity. Structural MRI focused on the medial temporal area showed stable predictive value throughout the 5-year course.	Non-consecutive recruitment; Readers were not blinded or no comment was made about the blinding of the readers; High percentage (> 25%) of people who dropped out of the study.

Kobayashi S, Makino K, Hatakeyama S, et al. The usefulness of combined brain perfusion single-photon emission computed tomography, Dopamine-transporter single-photon emission computed tomography, and 123 I-metaiodobenzylguanidine myocardial scintigraphy for the diagnosis of dementia with Lewy bodies. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society. 2017;17(4):247-55.	28130808	Comparative Study	low level of evidence	To evaluate the extent to which diagnostic accuracy can be increased by using different combinations of brain perfusion single-photon emission computed tomography (bp-SPECT), 123 I-metaiodobenzylguanidine myocardial scintigraphy (MIBG scintigraphy), and DAT-SPECT.	Thirty-four patients with probable DLB (75.0 +/- 8.3 years old; 14 men, 20 women) underwent bp-SPECT, MIBG scintigraphy, and DAT-SPECT.	The authors' comparison of three functional imaging techniques indicated that MIBG scintigraphy (79%) and Dopamine-transporter (DAT) SPECT (79%) had better sensitivity for characteristic abnormalities in DLB than bp-SPECT (53%). The combination of the three modalities could increase sensitivity for diagnosis of DLB to 100%. Additionally, the ratio of patients with rapid eye movement sleep behaviour disorder was significantly higher in the positive finding group on MIBG scintigraphy than in the negative finding group.	In terms of stand-alone diagnostic means, priority should be placed on MIBG scintigraphy or DAT-SPECT for the diagnosis of DLB. However, the authors' results suggest that the combination of bp-SPECT, MIBG scintigraphy, and DAT-SPECT increased the accuracy of the clinical diagnosis of DLB.	Readers were not blinded or no comment was made about the blinding of the readers; Single reader or no inter-reader reliability was calculated.
Kockum K, Lilja-Lund O, Larsson EM, Rosell M, Soderstrom L, Virhammar J, Laurell K. The idiopathic normal-pressure hydrocephalus Radscale: A radiological scale for structured evaluation. Eur J Neurol. 2018; 25(3):569-576.	29281156	Single-center, prospective, non-consecutive, multi-reader	moderate level of evidence	To construct a radiological scale, composed of morphological signs of iNPH, and compare it with clinical symptoms.	Using the Swedish population register, 1000 randomized individuals over the age of 65 years were invited to participate and to complete a questionnaire with seven questions on iNPH symptoms. A total of 673 individuals completed the questionnaire. Those who reported ≥2 symptoms (n = 117) and 51 randomly selected individuals with <2 symptoms participated in further investigations. Exclusion criteria were severe medical conditions sufficient to explain the symptoms, e.g. a known brain tumour. Other comorbidities, such as osteoarthritis, diabetes and hypertension, were common. Only three participants had been under investigation for iNPH, of which one declined operation. The final sample (n = 168) consisted of 93 (55%) females and 75 (45%) males with the same age distribution for both genders [mean age 75 (range, 66–92) years]. Of these, 127 were aged < 80 years and 41 were aged ≥ 80 years.	The 168 individuals underwent computed tomography of the brain and a neurological examination with assessment of clinical symptoms according to Hellstrom's iNPH scale. Two radiologists, blinded to clinical data, independently evaluated and measured eight radiological parameters, i.e. Evans' index, callosal angle, size of temporal horns, narrow high-convexity sulci, dilated Sylvian fissures, focally dilated sulci, periventricular hypodensities and bulging of the lateral ventricular roof.	In a linear regression model, all parameters except ventricular roof bulging were significantly associated with clinical iNPH symptoms. The seven remaining parameters were summarized into a total iNPH Radscale score ranging from 0 to 12. There was a significant correlation (r = 0.55, P < 0.001) between the total iNPH Radscale score and clinical symptoms. The inter-rater agreement for the included radiological parameters was high (intraclass correlation, 0.74–0.97). The authors conclude that the iNPH Radscale may become a valuable diagnostic screening tool, allowing a structured radiological assessment. A high iNPH Radscale score together with clinical symptoms should raise suspicion of iNPH, motivating further evaluation for shunt surgery	The study includes elderly people with substantial comorbidity and thus a wide range of reasons for gait, urinary and cognitive dysfunction. The correlation between symptoms and radiological signs would probably have been stronger in clinical material, with selected patients with iNPH and completely healthy controls. Secondly, for periventricular hypodensities and callosal angle, assessment with MRI would be superior to CT. Peri-ventricular oedema may sometimes be easier to differentiate from chronic ischemic lesions on MRI.
Kojoukhova M, Koivisto AM, Korhonen R, et al. Feasibility of radiological markers in idiopathic normal pressure hydrocephalus. Acta Neurochirurgica. 2015;157(10):1709-18; discussion 19.	26190755	Retrospective study	low level of evidence	To examine the usefulness of radiological markers in the diagnostics and prediction of shunt response in iNPH.	In this retrospective cohort study, the authors evaluated brain CT or MRI scans of 390 patients with suspected iNPH. Based on a 24-h intraventricular pressure monitoring session, patients were classified into a non-NPH (n=161) or probable iNPH (n=229) group. Volumes of cerebrospinal fluid compartments (lateral ventricles, sylvian and suprasylvian subarachnoid spaces and basal cisterns) were visually assessed. Disproportionally enlarged subarachnoid spaces, flow void, white matter changes, medial temporal lobe atrophy and focally dilated sulci were evaluated. Moreover, the authors measured quantitative markers: Evans' index (EI), the modified cella media index, mean width of the temporal horns and callosal angle.	iNPH was more likely in patients with severe volumetric disproportion between the suprasylvian and sylvian subarachnoid spaces than in those without disproportion (OR 7.5, CI 95 % 4.0-14.1, P<0.0001). Mild disproportion (OR 2.6, CI 95 % 1.4-4.6, P=0.001) and narrow temporal horns (OR per 1 mm 0.91, CI 95 % 0.84-0.98, P=0.014) were also associated with an iNPH diagnosis. Other radiological markers had little association with the iNPH diagnosis in the final combined multivariate model. Interestingly, EI was higher in non-NPH than iNPH patients (0.40 vs. 0.38, P=0.039). Preoperative radiological markers were not associated with shunt response.	Visually evaluated disproportion was the most useful radiological marker in iNPH diagnostics. Narrower temporal horns also supported an iNPH diagnosis, possibly since atrophy was more pronounced in the non-NPH than iNPH group.	Non-consecutive recruitment; Readers were not blinded or no comment was made about the blinding of the readers; There was a long time lag between the diagnostic test and the reference standard, long enough that the underlying disease may have significantly changed; Reference standard was inadequate.
Kramer J, Lueg G, Schiffler P, Vrachimis A, Weckesser M, Wenning C, Pawlowski M, Johnen A, Teuber A, Wersching H, Meuth SG, Duning T. Diagnostic value of diffusion tensor imaging and positron emission tomography in early stages of frontotemporal dementia. J Alzheimers Dis. 2018; 63(1):239-253.	29614640	Single-center, prospective, non-consecutive, multi-reader	low level of evidence	To investigate the diagnostic value of DTI in comparison to 18F-FDG-PET to detect cerebral alterations in a cohort of patients with early stages of bvFTD who were lacking frontal and temporal atrophy on conventional MRI.	Thirty patients with bvFTD were selected out of a total of 59 screened patients recruited from the memory disorder unit at the Department of Neurology at the University Hospital Muenster in Germany between 2011-2014. Only patients with early stages of bvFTD, that is a disease duration ≤ 36 months, a MMSE ≥15 points, and the absence of severe behavioural symptoms were included. Subjects with a history of other neurological disorders than bvFTD such as other types of dementia, other neurodegenerative disorders (Huntington's disease, multiple system atrophy, motor neuron disease), stroke, hydrocephalus, epilepsy, brain tumor, head injury, psychiatric illness not due to the dementia process (including drug or alcohol abuse), and other systemic diseases that interfere with cognitive functioning were excluded from the study. Further exclusion criteria were the intake of psychotropic drugs (e.g., antidementives including acetylcholinesterase inhibitors).	Patients underwent a detailed neuropsychological examination, cerebral 3T MRI with DTI analysis, and FDG-PET. After 12 months of follow-up, all patients finally fulfilled the diagnosis of bvFTD. Individual FDG-PET data analyses showed that 20 patients exhibited a "typical" pattern for bvFTD with bifrontal and/or temporal hypometabolism (bvFTD/PET+), and that 10 patients showed a "non-typical"/normal pattern (bvFTD/PET-). DTI data were compared with 42 healthy controls in an individual and voxel-based group analysis. To examine the clinical relevance of the findings, associations between pathologically altered voxels of DTI or FDG-PET results and behavioral symptoms were estimated by linear regression analyses.	DTI voxel-based group analyses revealed microstructural degeneration in bifrontal and bitemporal areas in bvFTD/PET+ and bvFTD/PET- groups. However, when comparing the sensitivity of individual DTI data analysis with FDG-PET, DTI appeared to be less sensitive. Neuropsychological symptoms were considerably related to neurodegeneration within frontotemporal areas identified by DTI and FDG-PET. The authors conclude that DTI seems to be an interesting tool for detection of functionally relevant neurodegenerative alterations in early stages of bvFTD, even in bvFTD/PET- patients. However, at a single subject level, it seems to be less sensitive than FDG-PET. Thus, improvement of individual DTI analysis is necessary.	The sample size of both groups was relatively small. Because the bvFTD/PET- group contains fewer patients than the bvFTD/PET+ group, all statistical analyses should be interpreted with caution. Moreover, the present study was performed in a cross-sectional setting, meaning interpretations of differences between groups as "changes" must be made with caution. Further longitudinal investigations including a larger group of patients and follow-up scans are warranted to investigate whether DTI might serve as marker for early disease detection, disease staging, and differentiation of bvFTD from other forms of dementia, e.g., atypical variants of Alzheimer's disease.
Laforce R, Jr., Buteau JP, Paquet N, et al. The value of PET in mild cognitive impairment, typical and atypical/unclear dementias: A retrospective memory clinic study. American Journal of Alzheimer's Disease & Other Dementias. 2010;25(4):324-32.	20539026	Research Support, Non-U.S. Gov't	low level of evidence	To examine the role of [(18)F]fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis of atypical/unclear dementias in a memory clinic setting.	A total of 94 patients with a diagnosis of mild cognitive impairment (MCI) or dementia, who had a PET study within 2 months of their diagnosis, were reevaluated at 5 and 18 months.	Results showed that PET was associated with a change in diagnosis in 29% of patients and a 64% increase in the use of cholinesterase inhibitors (ChEIs). PET significantly lowered the number of atypical/unclear diagnoses from 39.4% to 16% and nearly 30% of these were found to have a typical Alzheimer's disease (AD) pattern of hypometabolism.	The authors concluded that the addition of PET to the investigation of atypical/unclear cases of dementia helped generating a more accurate diagnosis and initiating earlier treatment. PET was of limited contribution to typical AD and frontotemporal dementia (FTD) cases. This study provides guiding evidence about the true value of PET imaging in the day-to-day challenge of dementia diagnosis.	Readers were not blinded or no comment was made about the blinding of the readers; Single reader or no inter-reader reliability was calculated.
Lan MJ, Ogden RT, Kumar D, et al. Utility of Molecular and Structural Brain Imaging to Predict Progression from Mild Cognitive Impairment to Dementia. Journal of Alzheimer's Disease. 2017;60(3):939-47.	28984586	Longitudinal study	moderate level of evidence	To compare three neuroimaging biomarkers to predict progression to dementia in subjects with mild cognitive impairment (MCI).	Eighty-eight subjects with MCI and 40 healthy controls (HCs) were recruited. Subjects had a 3T magnetic resonance imaging (MRI) scan, and two positron emission tomography (PET) scans, one with Pittsburgh compound B ([11C]PIB) and one with fluorodeoxyglucose ([18F]FDG). MCI subjects were followed for up to 4 y and progression to dementia was assessed on an annual basis.	MCI subjects had higher [11C]PIB binding potential (BPND) than HCs in multiple brain regions, and lower hippocampus volumes. [11C]PIB BPND, [18F]FDG standard uptake value ratio (SUVR), and hippocampus volume were associated with time to progression to dementia using a Cox proportional hazards model. [18F]FDG SUVR demonstrated the most statistically significant association with progression, followed by [11C]PIB BPND and then hippocampus volume. [11C]PIB BPND and [18F]FDG SUVR were independently predictive, suggesting that combining these measures is useful to increase accuracy in the prediction of progression to dementia. Hippocampus volume also had independent predictive properties to [11C]PIB BPND, but did not add predictive power when combined with the [18F]FDG SUVR data.	This work suggests that PET imaging with both [11C]PIB and [18F]FDG may help to determine which MCI subjects are likely to progress to AD, possibly directing future treatment options.	Non-consecutive recruitment; Readers were not blinded or no comment was made about the blinding of the readers; Single reader or no inter-reader reliability was calculated.

Meyer S, Mueller K, Stuke K, et al. Predicting behavioral variant frontotemporal dementia with pattern classification in multi-center structural MRI data. NeuroImage Clinical. 2017;14:656-62.	28348957	Multicenter Study; Research Support, Non-U.S. Gov't	low level of evidence	To validate the potential of imaging criteria to individually predict diagnosis with machine learning algorithms.	Brain atrophy was measured with structural magnetic resonance imaging (MRI) at 3 Tesla in a multi-centric cohort of 52 bvFTD patients and 52 healthy control subjects from the German FTLD Consortium's Study. Beside group comparisons, diagnosis bvFTD vs. controls was individually predicted in each subject with support vector machine classification in MRI data across the whole brain or in frontotemporal, insular regions, and basal ganglia known to be mainly affected based on recent meta-analyses. Multi-center effects were controlled for with a new method, "leave one center out" conjunction analyses, i.e. repeatedly excluding subjects from each center from the analysis.	Group comparisons revealed atrophy in, most consistently, the frontal lobe in bvFTD beside alterations in the insula, basal ganglia and temporal lobe. Most remarkably, support vector machine classification enabled predicting diagnosis in single patients with a high accuracy of up to 84.6%, where accuracy was highest in a region-of-interest approach focusing on frontotemporal, insular regions, and basal ganglia in comparison with the whole brain approach.	The authors' study demonstrates that MRI, a widespread imaging technology, can individually identify bvFTD with high accuracy in multi-center imaging data, paving the road to personalized diagnostic approaches in the future.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled; Non-consecutive recruitment; Single reader or no inter-reader reliability was calculated.
Miskin N, Patel H, Franceschi AM, et al. Diagnosis of Normal-Pressure Hydrocephalus: Use of Traditional Measures in the Era of Volumetric MR Imaging. Radiology. 2017;285(1):197-205.	28498794	Research Support, Non-U.S. Gov't; Research Support, N.I.H., Extramural	low level of evidence	To assess the diagnostic performance of the callosal angle (CA) and Evans index (EI) measures and to determine their role versus automated volumetric methods in clinical radiology.	Magnetic resonance (MR) examinations performed before surgery (within 1-5 months of the MR examination) in 36 shunt-responsive patients with normal-pressure hydrocephalus (NPH; mean age, 75 years; age range, 58-87 years; 26 men, 10 women) and MR examinations of age- and sex-matched patients with Alzheimer disease (n = 34) and healthy control volunteers (n = 36) were studied. Three blinded observers independently measured EI and CA for each patient. Volumetric segmentation of global gray matter, white matter, ventricles, and hippocampi was performed by using software. These measures were tested by using multivariable logistic regression models to determine which combination of metrics is most accurate in diagnosis.	The model that used CA and EI demonstrated 89.6%-93.4% accuracy and average area under the curve of 0.96 in differentiating patients with NPH from patients without NPH (ie, Alzheimer disease and healthy control). The regression model that used volumetric predictors of gray matter and white matter was 94.3% accurate.	CA and EI may serve as a screening tool to help the radiologist differentiate patients with NPH from patients without NPH, which would allow for designation of patients for further volumetric assessment.	Non-consecutive recruitment.
Ossenkoppele R, Rabinovici GD, Smith R, et al. Discriminative accuracy of [18F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. JAMA. 2018; 320(11):1151-1162.	30326496	Multi-center, prospective cross-sectional, multi-reader	moderate level of evidence	To examine the discriminative accuracy of [18F]flortaucipir for AD vs. non-AD neurodegenerative disorders.	Convenience sample of participants covering a wide range of neurodegenerative diseases was recruited from the Memory Disorder Clinic of Gangnam Severance Hospital (Seoul, South Korea), the Swedish BioFINDER study at Lund University (Lund, Sweden), and the University of California San Francisco (UCSF, United States) Alzheimer Disease Research Center who underwent [18F]flortaucipir PET between June 2014-November 2017. The study included 719 participants, including 179 with AD dementia, 254 with non-AD neurodegenerative disorder (Parkinson disease with [n = 70] or without [n = 23] cognitive impairment, progressive supranuclear palsy [n = 40], behavioral variant frontotemporal dementia [n = 33],dementia with Lewy bodies [n = 24], corticobasal syndrome [n = 23], nonfluent variant primary progressive aphasia [n = 17], semantic variant primary progressive aphasia [n = 11], vascular dementia [n = 7], multiple system atrophy [n = 3], chronic traumatic encephalopathy [n = 2], and unspecified primary progressive aphasia [n = 1]), 126 with MCI (83 [66%] with MCI due to AD), and 160 cognitively normal controls (147 research volunteers and 13 participants with subjective cognitive decline). The overall mean (SD) age was 68.8 (9.2) years and 48.4% were male.	The reference standard was the clinical diagnosis determined at the specialized memory centers. In the primary analysis, the discriminative accuracy (ie, sensitivity and specificity) of [18F]flortaucipir was examined for AD dementia vs all non-AD neurodegenerative disorders. In secondary analyses, the area under the curve (AUC) of [18F]flortaucipir SUVR was compared with 3 established magnetic resonance imaging measures (hippocampal volumes and AD signature and whole-brain cortical thickness), and sensitivity and specificity of [18F]flortaucipir in MCI due to AD vs non-AD neurodegenerative disorders were determined.	The proportions of patients who were amyloid-β positive were 26.3%, 65.9%, 100%, and 23.8% among cognitively normal controls, patients with MCI, patients with AD dementia, and patients with non-AD neurodegenerative disorders, respectively. [18F]flortaucipir uptake in the medial-basal and lateral temporal cortex showed 89.9% (95% CI, 84.6%-93.9%) sensitivity and 90.6% (95%CI, 86.3%-93.9%) specificity using the threshold based on controls (SUVR, 1.34), and 96.8% (95%CI, 92.0%-99.1%) sensitivity and 87.9% (95%CI, 81.9%-92.4%) specificity using the Youden Index–derived cutoff (SUVR, 1.27) for distinguishing AD dementia from all non-AD neurodegenerative disorders. The AUCs for all 5 [18F]flortaucipir ROIs were higher (AUC range, 0.92-0.95) compared with the 3 volumetric MRI measures (AUC range, 0.63-0.75; all ROIs P < .001). Diagnostic performance of the 5 [18F]flortaucipir ROIs were lower in MCI due to AD (AUC range, 0.75-0.84). The authors conclude that among patients with established diagnoses at a memory disorder clinic, [18F]flortaucipir PET was able to discriminate AD from other neurodegenerative diseases. The accuracy and potential utility of this test in patient care require further research in clinically more representative populations.	First, there is a potential selection bias because participants were recruited from academic memory disorder clinics and had already established diagnoses at time of [18F]flortaucipir PET scanning. Second, the clinical diagnosis served as reference standard, as there were only limited (n = 6 cases) autopsy data available. Future studies on clinicopathological relationships are essential, especially in tau-negative AD dementia and tau-positive non-AD disorders. Third, there is currently no consensus on the optimal methodology for determining tau positivity. Fourth, the multicenter approach has some inherent disadvantages related to lack of harmonization of both clinical and neuroimagingdata acquisition. Fifth, results obtained with [18F]flortaucipir might not be directly generalizable to other tau PET tracers given the differences in specificity and affinity between tracers.
Quaranta D, Gainotti G, Di Giuda D, et al. Predicting progression of amnesic MCI: The integration of episodic memory impairment with perfusion SPECT. Psychiatry Res Neuroimaging. 2018; 271:43-49.	29129545	Single-center, prospective, consecutive, multi-reader	low level of evidence	To assess if the association between results of the Episodic Memory Score (EMS) and of SPECT investigation could further improve the ability to predict conversion from amnesic MCI (aMCI) to AD.	The sample consisted of 42 Amnesic Mild Cognitive Impairment (aMCI) subjects (30 multiple domains – 21 plus dysexecutive impairment– 5 plus linguistic impairment – 2 plus impairment of visuospatial skills – 3 plus dysesecutive and linguistic impairment) as defined according to current clinical criteria. All patients were at their first visit and referred onset of the cognitive/memory disorders lasting no more than two years. Exclusion criteria were the following: a history of traumatic head injury, epilepsy, alcoholism or other major neurological or psychiatric diseases; medical conditions potentially associated with cognitive disturbances (i.e., renal or hepatic failure, thyroid dysfunction, folate and/or vitamin B12 deficits). mean age of 69.64 years (standard deviation [SD] = 7.251) and a mean education of 10.00 years (SD = 4.478).	Subjects underwent a baseline neuropsychological examination, which included the Mini-Mental State Examination (MMSE). For each subject the EMS was computed. During the 2-year follow-up period the patients underwent a complete neurological and medical examination, and a neuropsychological assessment every six months. Diagnoses at the follow-up examination were made by two neurologists who were blinded to results of both the baseline neuropsychological and SPECT examination. All patients underwent brain perfusion SPECT within two weeks from the baseline neuropsychological assessment.	At the final follow-up 15 subjects progressed to AD. The EMS predicted progression from aMCI to dementia with a high level of sensitivity and a lower level of specificity, but the association of neuropsychological (EMS) and SPECT data (hypoperfusion in the Posterior Cingulate Cortex) increased the accuracy in predicting conversion from aMCI to AD. The association of results obtained by aMCI patients on memory tests and perfusion SPECT may improve the accuracy in detecting subjects who will progress to dementia. The use of currently available and low-cost investigations could be advantageous in terms of public health policies.	The authors acknowledge that such level of diagnostic accuracy (90%) may not be considered sufficient in clinical practice, especially if it is compared to the standards used in other disciplines.
Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beenficiaries with mild cognitive impairment or dementia. JAMA. 2019; 321(13):1286-1294.	30938796	Multisite longitudinal prospective, non-consecutive, multi-reader	moderate level of evidence	To determine if amyloid PET is associated with subsequent changes in the management of patients with MCI or dementia of uncertain etiology.	Patients were recruited by dementia specialists from their clinical practices. Eligible patients were Medicare beneficiaries aged 65 or older, English or Spanish speaking,with a diagnosis of mild cognitive impairment (MCI) or dementia established by a dementia specialist within the past 24 months. Nine hundred forty-six dementia specialists from 595 unique practices across the United States participated in the study. Medicare beneficiaries (n = 16 008) were registered for the study aim reported in this article between February 8, 2016, and September 20, 2017; of these, 11 409 (71.3%) had complete information and were included in the final analysis data set. Patients were all required to meet appropriate use criteria for amyloid PET. Patients were excluded if amyloid status was already known based on prior PET or cerebrospinal fluid (CSF) analysis or if learning amyloid status could, in the opinion of the specialist, cause significant psychological harm. Among 16 008 registered participants, 11 409 (71.3%) completed study procedures and were included in the analysis (median age, 75 years [interquartile range, 71-80]; 50.9% women; 60.5% with MCI).	All patients were required to have completed a comprehensive diagnostic assessment, including global cognition assessed via the Mini-Mental State Examination (range, 0 [worst] to 30 [best]) or Montreal CognitiveAssessment (range, 0 [worst] to 30 [best]) at the time of enrollment, laboratory testing within the past 12 months, and head CT or MRI within the past 24 months. All participants underwent amyloid PET at 343 imaging centers. The primary end point was change in management between the pre- and post-PET visits, as assessed by a composite outcome that included Alzheimer disease drug therapy, other drug therapy, and counseling about safety and future planning. The study was powered to detect a 30% or greater change in the MCI and dementia groups. One of 2 secondary end points is reported: the proportion of changes in diagnosis (from Alzheimer disease to non–Alzheimer disease and vice versa) between pre- and post-PET visits.	Amyloid PET results were positive in 3817 patients with MCI (55.3%) and 3154 patients with dementia (70.1%). The composite end point changed in 4159 of 6905 patients with MCI (60.2%[95%CI, 59.1%-61.4%]) and 2859 of 4504 patients with dementia (63.5% [95%CI, 62.1%-64.9%]), significantly exceeding the 30% threshold in each group (P < .001, 1-sided). The etiologic diagnosis changed from Alzheimer disease to non–Alzheimer disease in 2860 of 11,409 patients (25.1%[95%CI, 24.3%-25.9%]) and from non–Alzheimer disease to Alzheimer disease in 1201 of 11,409 (10.5% [95%CI, 10.0%-11.1%]). The authors conclude that among Medicare beneficiaries with MCI or dementia of uncertain etiology evaluated by dementia specialists, the use of amyloid PET was associated with changes in clinical management within 90 days. Further research is needed to determine whether amyloid PET is associated with improved clinical outcomes.	First, the nonrandomized design and lack of a control group limit the direct attribution of changes in management to PET. Second, patients were included in the study based on criteria that "knowledge of PET results is expected to change diagnosis and management." Therefore, the a priori threshold for the rate of changes inmanagement could have been set higher than 30%. Third, observed changes in diagnosis and management represent the behavior of specialized physicians rather than evidence based standard of care.Fourth, this study did not directly compare the association between amyloid PET and changes in clinical management with management changes associated with other diagnostic tools, such as 18F-labeled fludeoxyglucose PET or CSF Alzheimer disease biomarkers. Fifth, based on third party report participants were primarily non-Hispanic white. Sixth, there were relatively high rates of protocol noncompliance, which likely reflect the practice-based setting of the study.

Rinne JO, Wong DF, Wolk DA, et al. [(18)F]Flutemetamol PET imaging and cortical biopsy histopathology for fibrillar amyloid beta detection in living subjects with normal pressure hydrocephalus: pooled analysis of four studies. Acta Neuropathologica. 2012;124(6):833-45.	23053137	Research Support, Non-U.S. Gov't	low level of evidence	To determine the level of association between uptake of the fibrillar amyloid beta positron emission tomography (PET) imaging agent [(18)F]flutemetamol (Pittsburgh Compound B analog with a 5.5 times longer half-life to enable it to be used in the clinical setting) and neuritic plaques and fibrillar amyloid beta measured by pathologic staining of cortical region biopsy samples.	Fifty-two patients with suspected normal pressure hydrocephalus underwent prospective (n = 30) or retrospective (n = 22) [(18)F]flutemetamol PET imaging for detection of cerebral cortical fibrillar amyloid beta and cortical brain biopsy during intracranial pressure measurement or ventriculo-peritoneal shunting. [(18)F]Flutemetamol uptake was quantified using standardized uptake value ratio (SUVR) with cerebellar cortex as the reference region. Tissue fibrillar amyloid beta was evaluated using immunohistochemical monoclonal antibody 4G8 and histochemical agents Thioflavin S and Bielschowsky silver stain, and an overall pathology result based on all available immunohistochemical and histochemical results. Biopsy site and contralateral [(18)F]flutemetamol SUVRs were significantly associated with neuritic plaque burden assessed with Bielschowsky silver stain (r (spearman's) = 0.61, p = 0.0001 for both), as was the composite SUVR with biopsy pathology (r (spearman's) = 0.74, p < 0.0001). SUVR and immunohistochemical results with 4G8 for detecting fibrillar amyloid beta were similar. Blinded image evaluation showed strong agreement between readers (kappa = 0.86). Overall sensitivity and specificity by majority read were 93 and 100 %. Noninvasive in vivo [(18)F]flutemetamol PET imaging demonstrates strong concordance with histopathology for brain fibrillar amyloid beta, supporting its promise as a tool to assist physicians with earlier detection of the disease process and making diagnostic decisions about concomitant AD and other diseases associated with brain amyloidosis.	Biopsy site and contralateral [(18)F]flutemetamol SUVRs were significantly associated with neuritic plaque burden assessed with Bielschowsky silver stain (r (spearman's) = 0.61, p = 0.0001 for both), as was the composite SUVR with biopsy pathology (r (spearman's) = 0.74, p < 0.0001). SUVR and immunohistochemical results with 4G8 for detecting fibrillar amyloid beta were similar. Blinded image evaluation showed strong agreement between readers (kappa = 0.86). Overall sensitivity and specificity by majority read were 93 and 100 %.	Noninvasive in vivo [(18)F]flutemetamol PET imaging demonstrates strong concordance with histopathology for brain fibrillar amyloid beta, supporting its promise as a tool to assist physicians with earlier detection of the disease process and making diagnostic decisions about concomitant AD and other diseases associated with brain amyloidosis.	Non-consecutive recruitment; Not all patients received the reference ("gold") standard or patients received different reference standards; There was a long time lag between the diagnostic test and the reference standard, long enough that the underlying disease may have significantly changed; Reference standard was inadequate; the biopsy procedure differed in the retrospective vs the prospective studies.
Staffaroni AM, Ljubenkov PA, Kornak J, et al. Longitudinal multimodal imaging and clinical endpoints for frontotemporal dementia clinical trials. Brian. 2019; 42(2):443-459.	30698757	Multi-center, retrospective, non-consecutive, single-reader	low level of evidence	To characterize longitudinal changes in patients with three frontotemporal dementia syndromes: bvFTD, and the semantic and non-fluent variants of primary progressive aphasia (PPA).	A total of 161 patients with FTD syndromes were included (77 with behavioural variant frontotemporal dementia 45 with semantic variant of PPA and 39 with non-fluent variant of PPA), along with 137 controls. Patients were studied at one of three medical centers: UCSF, Mayo Clinic, and Massachusetts General Hospital.	Patients were referred by outside physicians or self-referred, and all underwent neurological, neuropsychological and functional assessment with informant interview. All were diagnosed at a multidisciplinary consensus conference using published criteria: Neary criteria or the recently published consensus criteria for bvFTD and PPA, depending on year of enrolment. Visits included comprehensive neuropsychological and functional assessment, structural MRI (3 T), diffusion tensor imaging, and arterial spin labelled perfusion imaging. The goal was to identify measures that are appropriate as clinical trial outcomes for each group, as well as those that might be appropriate for trials that would include more than one of these groups. Linear mixed effects models were used to estimate changes in each measure, and to examine the correlation between imaging and clinical changes. Sample sizes were estimated based on the observed effects for theoretical clinical trials using bootstrapping techniques to provide 95% confidence intervals for these estimates.	Declines in functional and neuropsychological measures, as well as frontal and temporal cortical volumes and white matter microstructure were detected in all groups. Imaging changes were statistically significantly correlated with, and explained a substantial portion of variance in, the change in most clinical measures. Perfusion and diffusion tensor imaging accounted for variation in clinical decline beyond volume alone. Sample size estimates for atrophy and diffusion imaging were comparable to clinical measures. Corpus callosal fractional anisotropy led to the lowest sample size estimates for all three syndromes. The authors conclude that these findings provide further guidance on selection of trial endpoints for studies in frontotemporal dementia and support the use of neuroimaging, particularly structural and diffusion weighted imaging, as biomarkers. Diffusion and perfusion imaging appear to offer additional utility for explaining clinical change beyond the variance explained by volume alone, arguing for considering multimodal imaging in treatment trials.	In order to present a comprehensive view of the changes in clinical measures and multiple types of imaging and still maintain tractability for statistical analysis and readability, the authors chose only four large regions of interest and limited the analysis of DTI to fractional anisotropy. Future studies should examine potential differences in the utility of various DTI-based measures. The study used a standard two time point approach to power calculations, and the subgroups used for sample size calculations were smaller than those used for LME analyses, and varied depending on available data. Accordingly, direct comparison of sample sizes across measures, while informative and in broad agreement with previously published data, should be interpreted with caution as is evidenced by the sometimes very wide 95% confidence intervals.
Zwan MD, Bouwman FH, Konijnenberg E, et al. Diagnostic impact of [18F]flutemetamol PET in early-onset dementia. Alzheimer's Research & Therapy. 2017;9(1):2.	28093088	Clinical Trial; Multicenter Study	high level of evidence	To assess the diagnostic impact of the amyloid-positron emission tomography (PET) imaging agent [18F]flutemetamol in early-onset dementia patients, in terms of change in (confidence in) diagnosis and patient management plan.	This prospective bi-center study included 211 patients suspected of early-onset dementia who visited a tertiary memory clinic. Patients were eligible with Mini Mental State Examination>=18 and age at diagnosis<=70 years and in whom the diagnostic confidence was <90% after routine diagnostic work-up. All patients underwent [18F]flutemetamol PET, which was interpreted as amyloid-negative or amyloid-positive based on visual rating. Before and after disclosing the PET results, the authors assessed the diagnostic confidence (using a visual analog scale of 0-100%) and clinical diagnosis. The impact of [18F]flutemetamol PET on the patient management plan was also evaluated.	[18F]flutemetamol PET scans were positive in 133 out of 211 (63%) patients, of whom 110 out of 144 (76%) patients had a pre-PET Alzheimer's disease (AD) diagnosis and 23 out of 67 (34%) patients had a non-AD diagnosis. After disclosure of PET results, 41/211 (19%) diagnoses changed. Overall, diagnostic confidence increased from 69 +/- 12% to 88 +/- 15% after disclosing PET results (P<0.001; in 87% of patients). In 79 (37%) patients, PET results led to a change in patient management and predominantly the initiation of AD medication when PET showed evidence for amyloid pathology.	[18F]flutemetamol PET changed clinical diagnosis, increased overall diagnostic confidence, and altered the patient management plan. The authors' results suggest that amyloid PET may have added value over the standardized diagnostic work-up in early-onset dementia patients with uncertain clinical diagnosis. This study provides evidence for the recommendations put forward in the appropriate use criteria for amyloid PET in clinical practice.	Readers were not blinded or no comment was made about the blinding of the readers; Single reader or no inter-reader reliability was calculated.