A Clinician-Informed Translational Roadmap for PET-Free MRI-Based Amyloid-Beta Assessment in Alzheimer's Disease

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Abstract. Amyloid-β (Aβ) confirmation is increasingly important in early Alzheimer's disease pathways, but amyloid-PET imaging remains costly and difficult to scale. Recent PET-guided knowledge distillation has shown that PET-derived supervision can be transferred to an MRI-only student model for Aβ status prediction, preserving PET-free inference and avoiding non-imaging covariates such as APOE genotype or cognitive scores, which are often unavailable in routine clinical workflows. To support clinical translation beyond binary classification, this paper presents a clinician-informed translational roadmap outlining three extensions to an existing PET-guided MRI-only framework: continuous Centiloid-aware amyloid burden estimation, longitudinal conversion and prognosis modeling, and region-level interpretability. For each direction, the proposed output target, clinical use case, required data structure, validation metrics, and major confounders are defined. The proposed extensions define a structured design and evaluation plan for future MRI-only amyloid assessment systems, clarifying how PET-guided MRI models can move from binary screening toward outputs that are interpretable, clinically meaningful, and suitable for prospective validation.

Keywords: Alzheimer's disease · Amyloid-β · Centiloid · MRI · Knowledge distillation · Translational validation · Radiomics

1 Introduction

Alzheimer's disease (AD) is the predominant form of dementia. Approximately 57 million people were living with dementia globally in 2021 [30]. By 2030, this

number is projected to reach 78 million, with substantial social and economic implications [29]. The pathological hallmarks of AD include cerebral amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau [34]; longitudinal Aβ-PET evidence indicates that amyloid deposition can occur up to two decades before clinical symptoms manifest [27]. This pre-symptomatic time window offers a critical opportunity for secondary prevention research [23]. In parallel, accurate biomarker confirmation is increasingly important in early symptomatic pathways for anti-amyloid therapies such as lecanemab [25] and donanemab [24], both of which require confirmation of amyloid pathology before treatment initiation [20, 31].

In biomarker-based research and specialist clinical pathways, Aβ status is commonly assessed through positron emission tomography (PET) with amyloid-sensitive radiotracers such as ^{11}C-Pittsburgh Compound B and ^{18}F-florbetapir, or through cerebrospinal fluid assays [1, 10]. Amyloid PET provides quantitative, spatially resolved estimates of Aβ burden, and many modern quantitative amyloid-PET pipelines use the Centiloid (CL) scale to improve compatibility across analysis techniques and tracers [13]. However, amyloid PET is expensive, exposes patients to ionizing radiation, and is difficult to scale for population-level screening. In one health-economic model, routine amyloid-PET use at the mild cognitive impairment stage was not cost-effective [14]. In addition, the nuclear medicine community has projected that demand for amyloid PET could increase as much as 20-fold following the introduction of anti-amyloid therapies, creating a substantial bottleneck [9, 25].

By contrast, magnetic resonance imaging (MRI) is non-invasive, widely accessible, and recommended as a first-line neuroimaging modality in dementia assessment pathways [19, 26]. Although MRI does not directly visualize amyloid plaques, it captures structural, vascular, and tissue-level information that may reflect downstream or associated effects of neurodegenerative pathology, including medial temporal atrophy, white-matter signal abnormalities, and cerebrovascular burden [33]. For this reason, MRI-based Aβ prediction is of increasing interest as a potential screening or triage tool to identify individuals who may benefit from confirmatory PET or other biomarker testing [3, 11, 15].

PET-guided knowledge distillation has recently been proposed to transfer PET-derived supervision into MRI-only Aβ prediction without requiring PET, APOE genotype, or cognitive scores at inference; the reported framework achieved best Aβ classification AUCs of 0.74 on OASIS-3 and 0.68 on ADNI across four clinically available MRI contrasts [5]. In practice, this teacher–student strategy uses PET images during training to guide MRI representations, while relying on an MRI-only model during deployment.

These results support the technical feasibility of PET-free Aβ classification from standard clinical MRI, with further calibration and validation required before clinical deployment. The next translational research question is how this framework can support outputs more directly aligned with quantitative clinical interpretation, longitudinal decision-making, and anatomically grounded explanation. Building on this framework, this manuscript formalizes a clinician-

informed roadmap organized around three complementary directions: (i) continuous Centiloid-aware amyloid burden estimation, (ii) longitudinal conversion and prognosis modeling, and (iii) region-level interpretability based on anatomical parcellations and radiomic feature families, specifying clinically relevant endpoints, validation metrics, and potential confounders for each proposed direction, as a basis for subsequent implementation and validation studies.

2 Background: PET-Guided MRI-Only Amyloid Prediction

2.1 Existing MRI-Only Distillation Framework

The framework adopted as the methodological starting point is a PET-guided knowledge distillation approach for MRI-only Aβ classification, in which PET supervision is leveraged during training and inference is performed from MRI alone, without non-imaging covariates such as APOE genotype or cognitive scores [5]. Binary amyloid status is defined from PET-derived Centiloid values using a fixed positivity threshold, providing a tracer-harmonized label across cohorts [13]. At inference, only MRI volumes are required.

The image encoder is BiomedCLIP, a Vision Transformer pre-trained on 15M biomedical image-text pairs and adapted to the task through Low-Rank Adaptation applied to the upper transformer blocks. This encoder is shared between a teacher model that processes PET and MRI and a student model that processes MRI alone, with sagittal slice-level embeddings aggregated into a patient-level representation through multi-head attention pooling.

Training proceeds in three stages, with PET use restricted to teacher training. First, the teacher is supervised by the binary amyloid label, with PET as the query and MRI as the key and value in a cross-modal multi-head attention layer that learns PET–MRI alignment while extracting MRI features predictive of amyloid status. Second, the teacher model is refined through a Centiloid-aware contrastive objective, in which negative samples are selected online so that the anchor and negative in the triplet loss differ by at least a fixed Centiloid gap (5.0 CL in the original framework), encouraging the contrastive signal to reflect biochemically meaningful separation rather than visual similarity alone. Third, this PET-informed representation is distilled into an MRI-only student through feature-level alignment of ℓ_2-normalized embeddings and temperature-scaled logit distillation, jointly optimized with a margin-augmented classification loss.

This framework was evaluated on OASIS-3 and ADNI across four clinically available MRI contrasts (T1w, T2w, FLAIR, T2*) and their paired configurations, reaching best AUCs of 0.74 and 0.68, respectively, with cross-dataset transfer evaluated in both directions [5]. The present manuscript uses this separation between training-time PET supervision and MRI-only deployment to define clinically motivated output targets that extend this inference paradigm.

2.2 Translational Motivation

The framework summarized above establishes a technically feasible inference paradigm for PET-free Aβ classification. The translational question is how this paradigm can be extended toward outputs that better reflect the granularity of information used in clinical reasoning about amyloid pathology, treatment eligibility, and disease trajectory. Three translational gaps motivate the corresponding extension directions developed in Section 3.

Gap 1: From Binary Classification to Continuous Amyloid Burden. A binary Aβ^+/Aβ^- output collapses a continuous biological burden into a single threshold-based decision. In practice, amyloid imaging interpretation can benefit from quantitative Centiloid values alongside binary positivity, with recent AMYPAD consortium recommendations defining clinically relevant context-of-use ranges across the negative, intermediate, and positive regions of the scale [6]. This finer-grained burden information is relevant to biomarker-driven treatment pathways, since anti-amyloid therapies require confirmation of amyloid pathology, and quantitative amyloid-PET measures can support patient selection and treatment monitoring [6, 8]. Indeed, a binary MRI readout does not differentiate borderline subjects, who may lie close to the positivity threshold, from individuals with substantially elevated CL values. Extending the framework to predict a continuous Centiloid value would better reflect how amyloid burden is interpreted in current biomarker-driven pathways.

Gap 2: From Cross-Sectional Classification to Longitudinal Inference. The framework is designed for cross-sectional classification of present amyloid status from paired MRI–PET data. A natural translational extension is to address the temporal dimension of amyloid pathology: predicting whether and when an Aβ^- individual will progress toward Aβ^+ status. Amyloid accumulation is gradual, and reliable longitudinal change in Centiloid units requires follow-up intervals sufficient to exceed measurement variability [2]. A prognostic readout from MRI alone could move the framework from a present-state classifier toward a tool to be evaluated for triage, follow-up prioritization, and trial enrichment, with target populations including Aβ^- individuals, particularly those near the positivity threshold.

Gap 3: From Voxel-Level Saliency to Region-Level Interpretability. The post-training interpretability analysis in the existing framework is based on voxel-level saliency [22] and gradient-based class activation maps such as HiResCAM [7]. These maps provide post hoc attribution estimates of image regions associated with the prediction. In parallel, radiomic feature analyses on structural MRI have shown that histogram/first-order intensity and texture features extracted from anatomical regions can support Aβ positivity prediction [12]. These observations suggest that radiomic features and standard brain parcellations could serve as an interpretable layer on top of the existing model, beyond voxel attribution maps.

Together, these gaps define the scope of the translational roadmap developed in Section 3, while preserving the MRI-only inference constraint of the original framework.

3 Clinician-Informed Translational Roadmap

The three proposed directions share a common pivot: the patient-level MRI representation $e_i = f_\theta(x_i^{\mathrm{MRI}})$ produced by the MRI-only student of the existing PET-guided framework [5]. The first two directions extend this representation with task-specific output heads, whereas the third adds a region-level interpretability layer based on anatomical parcellations and radiomic feature families (Fig. 1). Across all directions, PET-derived measurements are used as target definitions, supervision, or retrospective validation, not as inputs at inference. Table 1 summarizes the clinical use cases, expected confounders, dataset requirements, and validation strategies considered in the roadmap.

Table 1. Use cases, confounders, data requirements, and validation targets for the three MRI-only translational directions.

Aspect	A: Continuous CL	B: Prognosis	C: Interpretability
Clinical use	Amyloid-burden stratification; triage for amyloid testing	Risk stratification; conversion triage; follow-up prioritization; trial enrichment	Anatomical reporting; ROI-level auditing
Confounders	Tracer/pipeline variability; CL imbalance; non-specific MRI changes	Small-vessel disease and age-related atrophy; technical CL variability; censoring	Parcellation choice; ROI registration; feature-extraction settings
Dataset use	MRI–PET–CL pairs	Longitudinal ≥ 2 PET timepoints	Same as A; atlas-based ROI extraction
Validation	MAE/RMSE; ρ vs. PET-CL; Bland–Altman; near-threshold error	td-AUC; C-index; td-Brier; calibration; MAE [CL/year]	T-S agreement; perturbations; surrogate fidelity; ROI stability

3.1 Continuous Centiloid-Aware Amyloid Burden Estimation

The first direction addresses Gap 1 by replacing the binary classification output with a continuous estimate of PET-derived amyloid burden. Since the original framework already exploits Centiloid values for label definition and CL-aware negative sampling [5], continuous CL estimation is a natural extension. Existing MRI-based amyloid assessment approaches have primarily focused on binary Aβ status prediction [3, 11, 12, 15], while the closest continuous-output deep-learning work either regresses PET standardized uptake value ratio (SUVR) from MRI with demographic and genetic covariates [28] or performs MRI-to-PET image synthesis followed by quantitative analysis of synthetic PET images

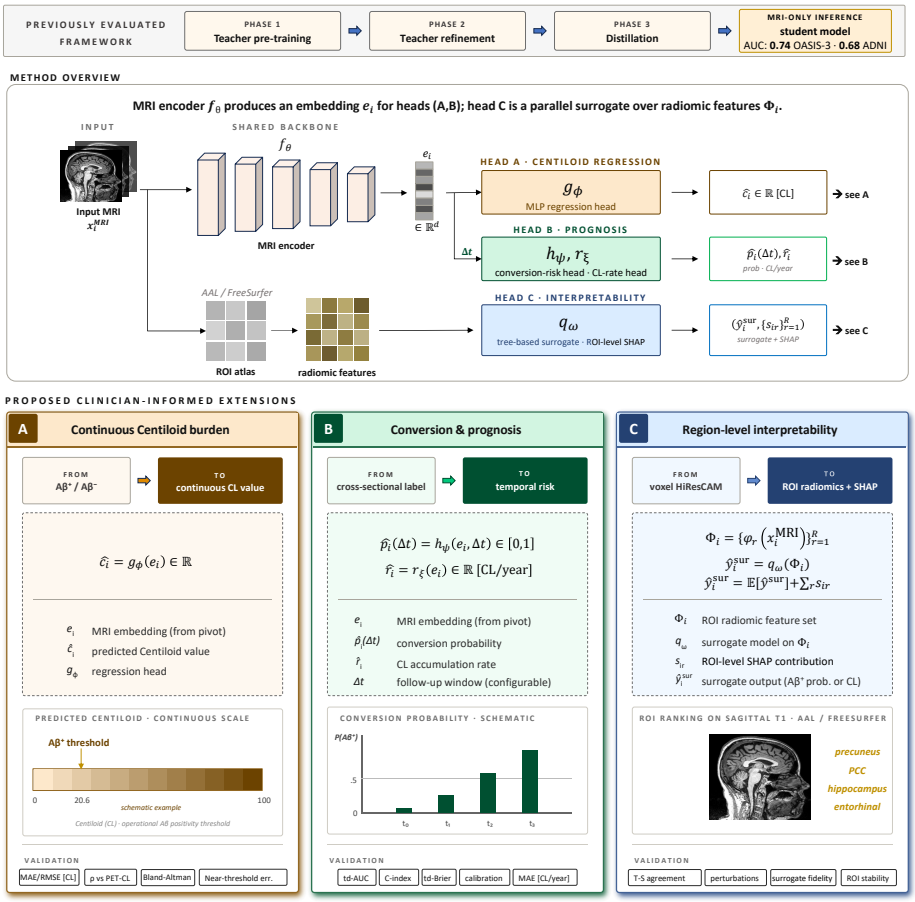

Fig. 1. Clinician-informed translational roadmap for extending a previously evaluated PET-guided MRI-only framework toward (A) continuous Centiloid estimation, (B) conversion and prognosis modeling, and (C) region-level interpretability. PET-derived data are used only for supervision or validation, never as inference inputs.

[4]. To our knowledge, continuous Centiloid regression from MRI alone, without PET-derived or non-imaging inputs at inference, has not been directly evaluated in prior deep-learning work.

Clinical Relevance and Technical Formulation. Recent AMYPAD context-of-use recommendations specify that low CL values are interpreted as excluding amyloid pathology with high certainty, high CL values correspond to pathological amounts, and intermediate values are associated with an increased risk of disease progression [6]. This continuous scale is also used in therapeutic trial analyses to quantify amyloid-PET change from baseline, with the magnitude of CL reduction serving as a quantitative measure of treatment effect on amyloid pathology [8].

Predicting a continuous CL value from MRI would yield a model output in the same scalar units used in clinical interpretation and treatment monitoring, supporting screening and triage before confirmatory amyloid testing.

Technically, the MRI-only student embedding e_i can be connected to a regression head g_ϕ that predicts $\hat{c}_i = g_\phi(e_i)$, the MRI-derived estimate of PET-CL. A closely related multimodal study regressed ^{18}F-florbetapir PET SUVR from MRI together with age, sex, and APOE genotype, trained with a mean squared error objective [28]. A direct analogue would be a mean-squared-error regression objective on PET-derived CL values, optionally combined with the binary classification loss in a multi-task formulation to preserve discrimination around the positivity threshold while supervising the full CL range.

Validation and Confounders. Validation should assess both continuous agreement and threshold-sensitive behavior, using MAE and RMSE in CL units, correlation ρ with PET-derived CL, and Bland–Altman plots for mean bias and limits of agreement, in line with deep-learning CL estimation from PET images [32]. Since errors are not equally impactful along the scale, performance should also be reported around the positivity threshold, where small numerical deviations can change the binary interpretation.

Three confounders are particularly relevant. Residual tracer- and pipeline-related variability persists when combining cohorts with different tracers, such as PiB and AV-45, despite CL harmonization [21]. Imbalance in CL distribution across cohorts can also bias a regression head toward more frequent target values, so the CL target distribution should be reported during validation. Finally, MRI-visible changes associated with age, small-vessel disease, or neurodegeneration may correlate with amyloid burden without being specific to amyloid pathology. Reported analyses should therefore include tracer-stratified evaluation, calibration around clinically relevant thresholds, and sensitivity analyses for demographic and vascular confounders.

3.2 Longitudinal Conversion and Prognosis Modeling

The second direction addresses Gap 2 by extending the framework from cross-sectional classification toward longitudinal prediction of amyloid trajectory. A clinically meaningful use case for a PET-free model is the identification of Aβ^- individuals near the positivity threshold, who may be at higher risk of conversion. Two complementary outputs are considered: conversion risk and annual Centiloid accumulation rate. Conversion is operationally defined, following the threshold used in the original framework, as the transition from baseline Aβ^- status (CL $\leq$ 20.6) to a follow-up visit with CL $>$ 20.6 [5].

Clinical Relevance and Technical Formulation. Prognostic estimates of amyloid conversion are relevant along the screening pathway that precedes anti-amyloid therapies. Real-world data from a tertiary memory clinic indicate that only a limited proportion of patients meet appropriate use recommendations for lecanemab and donanemab [20], supporting the need for scalable strategies to identify and

prioritize potential candidates before confirmatory amyloid PET. Participants in the intermediate Centiloid range, which AMYPAD recommendations associate with increased risk of disease progression [6], are a natural target population for this prognostic stratification, and an MRI-only prognostic readout could support follow-up prioritization.

Technically, the MRI-only student embedding e_i can be connected to two task-specific output heads. A first head h_ψ estimates the probability of conversion to Aβ^+ over a defined follow-up window Δt as $\hat{p}_i(\Delta t) = h_\psi(e_i, \Delta t) \in [0, 1]$, implemented either as fixed-window classification or as a time-to-event model. A second head r_ξ regresses the annual rate of Centiloid accumulation as $\hat{r}_i = r_\xi(e_i) \in \mathbb{R}$, expressed in CL/year, using subjects with at least two amyloid-PET measurements; prior amyloid-PET studies have shown that annual Centiloid accumulation can be measured reliably in cohorts with repeated PET acquisitions [2]. Both heads can be trained on the longitudinal subset and combined with the existing binary classification objective of the original framework [5].

Validation and Confounders. Validation should be aligned with the two output heads. For the conversion-probability head h_ψ, time-dependent AUC (td-AUC) at clinically relevant prediction horizons and the C-index quantify discrimination across the follow-up window, while calibration curves and the time-dependent Brier score quantify agreement between predicted probabilities and observed conversion, accounting for censoring when applicable. A prior deep-learning study used baseline hippocampal MRI to predict progression from mild cognitive impairment to Alzheimer's disease dementia and evaluated discrimination using the C-index and time-dependent ROC/AUC [16], supporting these survival-style metrics for MRI-based prognostic models. For the CL-rate head r_ξ, MAE in CL/year against longitudinal CL change should be reported, with stratification by baseline CL range to assess near-threshold behavior.

Three confounders are particularly relevant in the prognostic setting. Comorbid small-vessel disease and age-related atrophy can produce MRI signal changes overlapping neurodegenerative patterns and potentially influencing conversion probability and CL-rate estimates [33]; their distribution should therefore be reported and, where possible, modeled as covariates or used for stratification. Technical and biological factors, including quantification pipeline choices, radiotracer, harmonization status, age, and brain atrophy, can introduce systematic variability in Centiloid quantification [21], motivating sensitivity analyses across scanner and protocol subgroups. Finally, time-to-event analyses should account for incomplete follow-up, censoring before observed conversion, and possible competing risks, either under standard survival assumptions or with dedicated competing-risks models.

3.3 Region-Level Interpretability via Radiomics and SHAP

The third direction addresses Gap 3 by complementing voxel-level saliency and gradient-based activation maps with a region-level interpretability layer based on anatomical parcellations. Voxel-level maps indicate where the model attends in

image space, but clinical reasoning typically operates over AD-relevant anatomical regions, including early sites of Aβ accumulation such as the precuneus and posterior cingulate [18] and medial temporal regions such as the hippocampus and entorhinal cortex [33]. A region-level layer would express predictions in this same anatomical convention, supporting ROI-level model auditing alongside the voxel-level maps.

Technical Formulation and Validation. For each subject i, radiomic features $\Phi_i = \{\varphi_r(x_i^{\mathrm{MRI}})\}_{r=1}^{R}$ are extracted from atlas-defined regions, such as the Automated Anatomical Labeling (AAL) atlas, or from FreeSurfer-derived parcellations, where φ_r denotes the vector of descriptors extracted from region r. These descriptors include histogram/first-order intensity and texture features used in MRI-based amyloid analyses [12]. A tree-based surrogate model q_ω is trained on Φ_i to approximate the corresponding output of the main MRI-only model, either the binary Aβ^+ probability from the original classifier or the predicted CL value $\hat{c}_i$ from head g_ϕ, yielding $\hat{y}_i^{\mathrm{sur}} = q_\omega(\Phi_i)$. SHAP attribution is then used to explain the surrogate prediction [17]. Because SHAP values are first defined at feature level, the ROI-level contribution s_{ir} is obtained by aggregating the SHAP values of the radiomic features extracted from region r; in Fig. 1, s_{ir} denotes this aggregated per-ROI contribution. On the surrogate-output scale, this yields $\hat{y}_i^{\mathrm{sur}} = \mathbb{E}[\hat{y}^{\mathrm{sur}}] + \sum_r s_{ir}$. Validation should assess teacher–student regional agreement when both attributions are available in a common atlas space, sensitivity to localized perturbations, surrogate fidelity, and ROI ranking stability under resampling. Since radiomic features are sensitive to preprocessing, segmentation, and implementation choices [35], reporting should include parcellation choice, ROI registration quality, and feature-extraction settings.

4 Discussion and Conclusion

This paper formalizes a clinician-informed translational roadmap that extends an existing PET-guided MRI-only framework toward three complementary outputs: continuous Centiloid-aware amyloid burden estimation, longitudinal conversion and prognosis modeling, and region-level interpretability. The roadmap is built around the MRI-only inference paradigm of the existing pipeline [5]. Directions A and B reuse the patient-level MRI representation e_i through task-specific output heads, whereas Direction C adds a parallel radiomics-based surrogate layer over anatomical regions. Across all directions, PET-derived measurements are used for target definition, supervision, or retrospective validation, not as inference inputs. The roadmap specifies clinically relevant outputs, validation targets, and expected confounders while preserving the PET-free deployment constraint.

Limitations. This work is positioned as a clinician-informed roadmap, and the three directions outlined in Section 3 are presented as a proposed design and

evaluation plan, intended to be implemented and assessed in subsequent studies. The classification AUCs of the existing binary classifier [5] provide a starting point for this work, whereas the performance of the proposed extensions will need to be quantified in dedicated evaluation studies. The direction-specific confounders summarized in Table 1 and discussed in Sections 3.1–3.3 indicate where calibration, stratification, and sensitivity analyses should be prioritized in future evaluation studies. The proposed MRI-only outputs should be positioned as decision-support tools that can help prioritize confirmatory amyloid testing and follow-up, rather than as standalone diagnostic confirmation. Clinical use would require prospective validation against established amyloid biomarkers, such as amyloid PET, cerebrospinal fluid assays, or clinically validated plasma assays.

Translational Steps and Conclusion. A pragmatic next step is to evaluate each direction independently on retrospective subsets of datasets such as OASIS-3 and ADNI that satisfy the data requirements in Table 1, followed by external validation on independent clinical cohorts and analyses stratified by tracer, scanner, and baseline CL range. Among the three directions, continuous Centiloid estimation is the most immediate translational next step, as it preserves the cross-sectional MRI–PET data structure of the original framework while producing an output that aligns with quantitative amyloid-PET interpretation. Clinician feedback on the proposed outputs is particularly important for determining whether a continuous Centiloid estimate, a conversion-risk estimate, or a ranked ROI-level explanation is most useful for screening, triage, follow-up planning, or model auditing. By defining continuous Centiloid estimation, longitudinal conversion and prognosis modeling, and region-level interpretability as distinct but complementary directions, this manuscript provides a structured basis for future evaluation studies aimed at moving MRI-only Aβ assessment toward outputs that are interpretable, Centiloid-aware, and prognostically informative.

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References

1. Bao, W., Xie, F., Zuo, C., Guan, Y., Huang, Y.H.: PET Neuroimaging of Alzheimer's Disease: Radiotracers and Their Utility in Clinical Research. Frontiers in Aging Neuroscience **13** (May 2021). https://doi.org/10.3389/fnagi.2021.624330
2. Bollack, A., Collij, L.E., García, D.V., Shekari, M., Altomare, D., Payoux, P., Dubois, B., Grau-Rivera, O., Boada, M., Marquié, M., Nordberg, A., Walker, Z., Scheltens, P., Schöll, M., Wolz, R., Schott, J.M., Gismondi, R., Stephens, A., Buckley, C., Frisoni, G.B., Hanseeuw, B., Visser, P.J., Vandenberghe, R., Drzezga, A., Yaqub, M., Boellaard, R., Gispert, J.D., Markiewicz, P., Cash, D.M., Farrar, G., Barkhof, F.: Investigating reliable amyloid accumulation in Centiloids: Results from the AMYPAD Prognostic and Natural History Study. Alzheimer's & Dementia **20**(5), 3429–3441 (Apr 2024). https://doi.org/10.1002/alz.13761
3. Chattopadhyay, T., Ozarkar, S.S., Buwa, K., Joshy, N.A., Komandur, D., Naik, J., Thomopoulos, S.I., Ver Steeg, G., Ambite, J.L., Thompson, P.M.: Comparison of deep learning architectures for predicting amyloid positivity in Alzheimer's disease, mild cognitive impairment, and healthy aging, from T1-weighted brain structural MRI. Frontiers in Neuroscience **18** (Jul 2024). https://doi.org/10.3389/fnins.2024.1387196
4. Chen, Z., Bi, S., Shan, Y., Wang, F., Wang, Y., Qi, Z., Wang, T., Li, X., Li, S., Xiao, H., Wang, S., Cui, B., Qi, Z., Han, Y., Yan, S., Lu, J., for the Alzheimer's Disease Neuroimaging Initiative: MRI-to-PET synthesis via deep learning for amyloid-β quantification in Alzheimer's disease. European Radiology **36**(6), 5125–5137 (Jan 2026). https://doi.org/10.1007/s00330-025-12251-3
5. Chiumento, F., Dietlmeier, J., Killeen, R.P., Curran, K.M., O'Connor, N.E., Liu, M.: Cross-Modal Knowledge Distillation for PET-Free Amyloid-Beta Detection from MRI. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition (CVPR) Workshops. pp. 6164–6175 (Jun 2026)
6. Collij, L.E., Bollack, A., La Joie, R., Shekari, M., Bullich, S., Roé-Vellvé, N., Koglin, N., Jovalekic, A., Garciá, D.V., Drzezga, A., Garibotto, V., Stephens, A.W., Battle, M., Buckley, C., Barkhof, F., Farrar, G., Gispert, J.D.: Centiloid recommendations for clinical context-of-use from the AMYPAD consortium. Alzheimer's & Dementia **20**(12), 9037–9048 (Nov 2024). https://doi.org/10.1002/alz.14336
7. Draelos, R.L., Carin, L.: Use HiResCAM instead of Grad-CAM for faithful explanations of convolutional neural networks (Nov 2021). https://doi.org/10.48550/arXiv.2011.08891
8. van Dyck, C.H., Swanson, C.J., Aisen, P., Bateman, R.J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L.D., Iwatsubo, T.: Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine **388**(1), 9–21 (Jan 2023). https://doi.org/10.1056/NEJMoa2212948
9. Garibotto, V., Albert, N.L., Barthel, H., van Berckel, B., Boellaard, R., Brendel, M., Cecchin, D., Ekmekcioglu, O., van de Giessen, E., Guedj, E., Lammerstma, A.A., Semah, F., Traub-Weidinger, T., Van Weehaeghe, D., Morbelli, S., for the EANM Neuroimaging Committee: The approval of a disease-modifying treatment for Alzheimer's disease: Impact and consequences for the nuclear medicine community. European Journal of Nuclear Medicine and Molecular Imaging **48**(10), 3033–3036 (Sep 2021). https://doi.org/10.1007/s00259-021-05485-y
10. Hansson, O.: Biomarkers for neurodegenerative diseases. Nature Medicine **27**(6), 954–963 (Jun 2021). https://doi.org/10.1038/s41591-021-01382-x

11. Kim, D., Ottesen, J.A., Kumar, A., Ho, B.C., Bismuth, E., Young, C.B., Mormino, E., Zaharchuk, G.: Deep Learning-Based Prediction of PET Amyloid Status Using MRI. AJNR. American journal of neuroradiology **46**(12), 2590–2598 (Dec 2025). https://doi.org/10.3174/ajnr.A8899
12. Kim, J.P., Kim, J., Jang, H., Kim, J., Kang, S.H., Kim, J.S., Lee, J., Na, D.L., Kim, H.J., Seo, S.W., Park, H.: Predicting amyloid positivity in patients with mild cognitive impairment using a radiomics approach. Scientific Reports **11**(1), 6954 (Mar 2021). https://doi.org/10.1038/s41598-021-86114-4
13. Klunk, W.E., Koeppe, R.A., Price, J.C., Benzinger, T., Devous, M.D., Jagust, W., Johnson, K., Mathis, C.A., Minhas, D., Pontecorvo, M.J., Rowe, C.C., Skovronsky, D., Mintun, M.: The Centiloid Project: Standardizing Quantitative Amyloid Plaque Estimation by PET. Alzheimer's & dementia : the journal of the Alzheimer's Association **11**(1), 1–15.e4 (Jan 2015). https://doi.org/10.1016/j.jalz.2014.07.003
14. Lee, Y.S., Youn, H., Jeong, H.G., Lee, T.J., Han, J.W., Park, J.H., Kim, K.W.: Cost-effectiveness of using amyloid positron emission tomography in individuals with mild cognitive impairment. Cost Effectiveness and Resource Allocation **19**(1), 50 (Aug 2021). https://doi.org/10.1186/s12962-021-00300-9
15. Lew, C.O., Zhou, L., Mazurowski, M.A., Doraiswamy, P.M., Petrella, J.R., Alzheimer's Disease Neuroimaging Initiative: MRI-based Deep Learning Assessment of Amyloid, Tau, and Neurodegeneration Biomarker Status across the Alzheimer Disease Spectrum. Radiology **309**(1) (Oct 2023). https://doi.org/10.1148/radiol.222441
16. Li, H., Habes, M., Wolk, D.A., Fan, Y., Alzheimer's Disease Neuroimaging Initiative, Australian Imaging Biomarkers and Lifestyle Study of Aging: A deep learning model for early prediction of Alzheimer's disease dementia based on hippocampal magnetic resonance imaging data. Alzheimer's & dementia : the journal of the Alzheimer's Association **15**(8), 1059–1070 (Aug 2019). https://doi.org/10.1016/j.jalz.2019.02.007
17. Lundberg, S.M., Lee, S.I.: A unified approach to interpreting model predictions. In: Proceedings of the 31st International Conference on Neural Information Processing Systems. pp. 4768–4777. NIPS'17, Curran Associates Inc., Red Hook, NY, USA (Dec 2017)
18. Palmqvist, S., Schöll, M., Strandberg, O., Mattsson, N., Stomrud, E., Zetterberg, H., Blennow, K., Landau, S., Jagust, W., Hansson, O.: Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nature Communications **8**, 1214 (Oct 2017). https://doi.org/10.1038/s41467-017-01150-x
19. Raji, C.A., Benzinger, T.L.S.: The Value of Neuroimaging in Dementia Diagnosis. Continuum (Minneapolis, Minn.) **28**(3), 800–821 (Jun 2022). https://doi.org/10.1212/CON.0000000000001133
20. Rosenberg, A., Solomon, A., Bonnard, A., Daniilidou, M., Hagman, G., Hall, A., Matton, A., Öhlund-Wistbacka, U., Westman, E., Kivipelto, M.: Preparing for the implementation of anti-amyloid therapies in Europe: Assessing real-world eligibility for lecanemab and donanemab in a Swedish memory clinic. The Journal of Prevention of Alzheimer's Disease **13**(3), 100476 (Jan 2026). https://doi.org/10.1016/j.tjpad.2025.100476
21. Shekari, M., Vállez García, D., Collij, L.E., Altomare, D., Heeman, F., Pemberton, H., Roé Vellvé, N., Bullich, S., Buckley, C., Stephens, A., Farrar, G., Frisoni, G., Klunk, W.E., Barkhof, F., Gispert, J.D.: Stress testing the Centiloid: Precision and

variability of PET quantification of amyloid pathology. Alzheimer's & Dementia **20**(8), 5102–5113 (Jul 2024). https://doi.org/10.1002/alz.13883
22. Simonyan, K., Vedaldi, A., Zisserman, A.: Deep Inside Convolutional Networks: Visualising Image Classification Models and Saliency Maps (Apr 2014). https://doi.org/10.48550/arXiv.1312.6034
23. Sperling, R., Mormino, E., Johnson, K.: The evolution of preclinical Alzheimer's disease: Implications for prevention trials. Neuron **84**(3), 608–622 (Nov 2014). https://doi.org/10.1016/j.neuron.2014.10.038
24. U.S. Food and Drug Administration: KISUNLA (donanemab-azbt) injection, for intravenous use: Prescribing Information (2024)
25. Verger, A., Yakushev, I., Albert, N.L., van Berckel, B., Brendel, M., Cecchin, D., Fernandez, P.A., Fraioli, F., Guedj, E., Morbelli, S., Tolboom, N., Traub-Weidinger, T., Van Weehaeghe, D., Barthel, H.: FDA approval of lecanemab: The real start of widespread amyloid PET use? - the EANM Neuroimaging Committee perspective. European Journal of Nuclear Medicine and Molecular Imaging **50**(6), 1553–1555 (May 2023). https://doi.org/10.1007/s00259-023-06177-5
26. Vernooij, M.W., Pizzini, F.B., Schmidt, R., Smits, M., Yousry, T.A., Bargallo, N., Frisoni, G.B., Haller, S., Barkhof, F.: Dementia imaging in clinical practice: A European-wide survey of 193 centres and conclusions by the ESNR working group. Neuroradiology **61**(6), 633–642 (2019). https://doi.org/10.1007/s00234-019-02188-y
27. Villemagne, V.L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K.A., Salvado, O., Szoeke, C., Macaulay, S.L., Martins, R., Maruff, P., Ames, D., Rowe, C.C., Masters, C.L.: Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. The Lancet Neurology **12**(4), 357–367 (Apr 2013). https://doi.org/10.1016/S1474-4422(13)70044-9
28. Wang, C., Zhang, W., Ni, M., Wang, Q., Liu, C., Dai, L., Zhang, M., Shen, Y., Gao, F.: Deep-learning based multi-modal models for brain age, cognition and amyloid pathology prediction. Alzheimer's Research & Therapy **17**, 126 (2025). https://doi.org/10.1186/s13195-025-01773-z
29. World Health Organization: Global status report on the public health response to dementia. https://www.who.int/publications/i/item/9789240033245 (2021)
30. World Health Organization (WHO): Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia (2025)
31. Yakushev, I., Verger, A., Brendel, M., Cecchin, D., Fernandez, P.A., Fraioli, F., Grimmer, T., Tolboom, N., Traub-Weidinger, T., Guedj, E., Van Weehaeghe, D.: Lecanemab approval in EU: What should we be ready for?– the EANM perspective. European Journal of Nuclear Medicine and Molecular Imaging **52**(5), 1607–1610 (2025). https://doi.org/10.1007/s00259-025-07066-9
32. Yamao, T., Miwa, K., Kaneko, Y., Takahashi, N., Miyaji, N., Hasegawa, K., Wagatsuma, K., Kamitaka, Y., Ito, H., Matsuda, H.: Deep Learning-Driven Estimation of Centiloid Scales from Amyloid PET Images with 11C-PiB and 18F-Labeled Tracers in Alzheimer's Disease. Brain Sciences **14**(4), 406 (Apr 2024). https://doi.org/10.3390/brainsci14040406
33. Young, P.N.E., Estarellas, M., Coomans, E., Srikrishna, M., Beaumont, H., Maass, A., Venkataraman, A.V., Lissaman, R., Jiménez, D., Betts, M.J., McGlinchey, E., Berron, D., O'Connor, A., Fox, N.C., Pereira, J.B., Jagust, W., Carter, S.F., Paterson, R.W., Schöll, M.: Imaging biomarkers in neurodegeneration: Current and future practices. Alzheimer's Research & Therapy **12** (Apr 2020). https://doi.org/10.1186/s13195-020-00612-7

34. Zhang, J., Zhang, Y., Wang, J., Xia, Y., Zhang, J., Chen, L.: Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies. Signal Transduction and Targeted Therapy **9**(1), 211 (Aug 2024). https://doi.org/10.1038/s41392-024-01911-3
35. Zwanenburg, A., Vallières, M., Abdalah, M.A., Aerts, H.J.W.L., Andrearczyk, V., Apte, A., Ashrafinia, S., Bakas, S., Beukinga, R.J., Boellaard, R., Bogowicz, M., Boldrini, L., Buvat, I., Cook, G.J.R., Davatzikos, C., Depeursinge, A., Desseroit, M.C., Dinapoli, N., Dinh, C.V., Echegaray, S., El Naqa, I., Fedorov, A.Y., Gatta, R., Gillies, R.J., Goh, V., Götz, M., Guckenberger, M., Ha, S.M., Hatt, M., Isensee, F., Lambin, P., Leger, S., Leijenaar, R.T., Lenkowicz, J., Lippert, F., Losnegård, A., Maier-Hein, K.H., Morin, O., Müller, H., Napel, S., Nioche, C., Orlhac, F., Pati, S., Pfaehler, E.A., Rahmim, A., Rao, A.U., Scherer, J., Siddique, M.M., Sijtsema, N.M., Socarras Fernandez, J., Spezi, E., Steenbakkers, R.J., Tanadini-Lang, S., Thorwarth, D., Troost, E.G., Upadhaya, T., Valentini, V., van Dijk, L.V., van Griethuysen, J., van Velden, F.H., Whybra, P., Richter, C., Löck, S.: The Image Biomarker Standardization Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping. Radiology **295**(2), 328–338 (May 2020). https://doi.org/10.1148/radiol.2020191145