QUIC Amyloid PET Quantification – Implementation Roadmap

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1. Clinical Background

Alzheimer disease (AD) is the most common cause of dementia, affecting an estimated 6.9 million people aged 65 years and older in the United States as of 2024, a number projected to rise to nearly 14 million by 2060 due to population aging. Alzheimer's disease–related dementias (ADRD) include other progressive neurodegenerative disorders such as Lewy body disease, frontotemporal lobar degeneration, and cerebrovascular disease, each with overlapping symptoms and signs but distinct pathophysiologies. The societal burden of AD/ADRD is substantial, with annual costs in the U.S. estimated to exceed $345 billion, driven largely by costs associated with long-term care and loss of independence. Early and accurate diagnosis of AD/ADRD is critical for timely intervention, appropriate care planning, advancement of clinical trials, and increasingly initiation of disease-modifying therapies and response assessment monitoring.

Beta-amyloid (Aβ) deposition is one of the earliest pathological hallmarks of AD, preceding clinical symptoms by as much as two decades. It is a core component of the AT(N) framework for classifying AD biomarker profiles, where "A" denotes amyloid pathology as detected by PET or cerebrospinal fluid assays[1]. Detection of Aβ burden supports differentiation of AD from non-AD dementias, improves diagnostic confidence, and informs prognosis. The ability to quantify amyloid burden has additional implications for monitoring disease progression and evaluating treatment efficacy, especially in the era of anti-amyloid monoclonal antibodies.

The Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study and its successor New IDEAS have provided robust, real-world evidence supporting the clinical utility of amyloid PET (Aβ-PET)[2]. In IDEAS, Aβ-PET led to a change in management in 60% of cognitively impaired patients with uncertain etiology, impacting both diagnostic accuracy and treatment decisions. New IDEAS is expanding this work by focusing on more diverse patient populations and integrating amyloid PET into broader clinical workflows[3].

These large-scale, multicenter studies have catalyzed the transition of Aβ-PET from a research tool to a reimbursed clinical service in specific scenarios, with applications now extending to patient selection for anti-amyloid clinical trials and integration into the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) for post-marketing therapy monitoring[4].

With recent FDA approvals of disease-modifying anti-amyloid monoclonal antibodies such as lecanemab[5] and donanemab[6], Aβ-PET has assumed a central role in confirming pathology before treatment initiation. This is essential for meeting therapeutic eligibility criteria, minimizing unnecessary exposure, and ensuring payer reimbursement[7,8].

In the future, quantitative Aβ-PET may also support longitudinal assessment of treatment response, guide therapy discontinuation decisions, and facilitate head-to-head comparison of therapeutic agents.

2. Stakeholders

Successful implementation of quantitative Aβ-PET in clinical practice requires engagement from a broad and multidisciplinary stakeholder network. Each group brings unique expertise and perspectives that can shape protocol development, standardization, and adoption.

a. Neuroradiologists

Neuroradiologists are integral to integration of quantitative amyloid PET measures into clinical practice, and critical to showcasing how quantitative measures may improve interpretation of Aβ-PET findings[9]. This is particularly true when interpreting Aβ-PET together with structural MRI findings, providing an opportunity for neuroradiologists' subject matter expertise in CNS anatomy and physiology to inform the relationship between Aβ-PET results and potentially relevant changes brain structure (e.g., acceleration / deceleration of atrophy; structural changes implying alternate causes of dementia; amyloid-related imaging abnormalities (ARIA) in patients receiving anti-amyloid agents).

b. Nuclear medicine physicians

This domain has traditionally been led by nuclear medicine physicians, whose specialized expertise in radiopharmaceuticals and their imaging applications is essential. As demand for molecular imaging grows, the existing workforce shortages in nuclear medicine are likely to become more pronounced[10]. Addressing this challenge will require greater cross-specialty collaboration, particularly with neuroradiology and other imaging subspecialties.

c. Radiology and nuclear medicine residents and fellows

Post-graduate trainees in radiology and nuclear medicine represent the future workforce in neuroradiology. Accordingly, long-term efforts to integrate quantitative amyloid PET in clinical practice rests upon the ability to inspire and equip the next generation of radiologists in the interpretation, application, and clinical relevance of quantitative PET metrics. Beyond training, radiology residents and fellows bring unique perspectives to clinical care that are integral to advancing clinical research, protocol development, and "best practices" in quantitative Aβ-PET imaging. Early and consistent involvement of trainees in efforts to adapt and apply quantitative Aβ-PET in clinical practice is essential to ensure that this emergent technology is effectively integrated into clinical and research workflows.

d. Neurologists

Neurologists are central to the clinical evaluation, follow-up, and treatment of patients with cognitive impairment. In these roles, they order and interpret tests, counsel patients concerning treatment options, prescribe therapies, and assess response to interventions. Accordingly, their expertise is essential to inform the appropriate use of quantitative Aβ-PET, including diagnostic and treatment decisions (including starting and stopping therapies), and to support effective multidisciplinary collaboration required. As leaders in clinical neuroscience, neurologists are uniquely positioned to champion the responsible and effective use of quantitative amyloid PET imaging in clinical practice and to work together with colleagues in radiology and nuclear medicine to ensure that increasingly advanced imaging technologies are applied to enhance diagnostic accuracy and patient outcomes.

e. PCPs

Primary care practitioners are the first point of contact for patients with emergent cognitive concerns, supporting early recognition, risk stratification, and longitudinal care of patients with cognitive concerns. In these roles, they coordinate evaluations (including specialty referrals) and support longitudinal follow-up. In rural and other resource-limited settings, primary care practitioners may play an outsized role in the diagnosis and treatment of dementia – a reality that is likely to increase if the number of patients affected continues to outpace the capacity of dementia specialists. Accordingly, it is important that PCPs understand the clinical utility, interpretation, and limitations of quantitative Aβ-PET imaging, and that they are involved in the development and dissemination of appropriate use recommendations for clinical practice.

f. Imaging scientists

Imaging scientists are essential to ensure that image acquisition, processing, and quantification methods are robust, reproducible, and clinically meaningful. In partnership with clinicians, imaging scientists help translate complex data into actionable insights, enabling more precise diagnosis and monitoring of neurodegenerative diseases. Additionally, their role in training, quality assurance, and innovation supports the continuous improvement and deployment of imaging workflows (in partnership with neuroradiologist, nuclear medicine physicians, trainees, and technologists), and fosters the integration of emerging technologies, including artificial intelligence and machine learning.

g. Informaticists

Informaticists are critical to the integration of amyloid PET quantification tools and outputs into PACS, EMRs, and research databases as well to the development and implementation of decision-support tools integrating neuroimaging findings and evidence-based recommendations developed in partnership with clinical stakeholders and patient advocates. Engagement of informaticists is integral to support automated, reproducible workflows and structured reporting to advance clinical and research applications of quantitative amyloid PET imaging.

h. Technologists

Technologists serve as the operational backbone of the imaging workflow, ensuring consistency across scans, troubleshooting technical issues, and maintaining safety standards. Their precision in patient preparation, scanner calibration, and protocol adherence directly impacts image quality and the reliability of quantitative metrics. For these reasons, technologist engagement in implementation efforts is essential to generate reproducible and clinically actionable results. As frontline professionals, their insight and

experiences is also essential to iteratively improve enhance workflow efficiency, optimize patient experience, and support clinical rollout.

i. Patient advocates

Patients, care partners, care organizations, and other advocates drive demand for and utilization of diagnostic and therapeutic tools[2,11]. Their voice across the stages of technology development and implementation is important to ensure that quantitative Aβ-PET measures are adapted to meet patient care needs, promote informed treatment decisions, and expand access to appropriate care. Effective and consistent engagement of patient advocates can also promote education of healthcare professionals, patients, and other care partners concerning the benefits and limitations of quantitative Aβ-PET imaging, advancing shared decision making.

j. Insurance

Insurance providers and other payers shape access and reimbursement policies that ultimately dictate affordability and, by extension, access to advanced technologies in patient care. For these reasons, it is essential to convey to insurance providers how broader deployment of quantitative amyloid PET may improve diagnostic accuracy, guide accurate treatment decisions (including initiation and stopping of disease-specific therapies), and improve outcomes for patients and ultimately reduce the staggering long-term healthcare costs associated with management of AD/ADRD[8]. Insurer engagement, together with other stakeholders, is also essential to develop transparent, equitable criteria for coverage required to facilitate broad access to advanced imaging technologies.

k. Vendors

Vendors are key stakeholders in the implementation of quantitative amyloid PET imaging, as they provide the hardware, software, and technical support to enable high-quality, accessible image acquisition and analysis. Their collaboration with clinical teams and other frontline users is essential to tailor imaging platforms that meet specific diagnostic needs, ensure compatibility with EHRs, facilitate seamless integration into clinical workflows. Vendors also play a crucial role in training users, maintaining equipment, and driving innovation through ongoing product development and feedback loops required to keep pace with evolving standards in neuroimaging and dementia care.

3. State-of-the art in clinical Aβ-PET acquisition and interpretation protocols

Three Aβ-PET radiotracers have received FDA approval for clinical use in the United States. [F18]Florbetapir was the first agent approved in 2012, followed by [F18]Flutemetamol in 2013, and [F18]Florbetaben in 2014. Each of these tracers was initially approved by the FDA for PET imaging of the brain to estimate Aβ neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. In 2025, the FDA revised the labels of all three tracers to include use in selection of patients who are indicated for Aβ-directed therapy as described in the prescribing information of the therapeutic products. Aβ-PET was rarely utilized in clinical practice during the first decade following FDA approval, in large part due to a Centers for Medicare and Medicaid Services (CMS) national coverage determination (NCD) that provided reimbursement for the procedure under only very limited circumstances, a precedent then followed by commercial insurers. This situation changed with reversal of the NCD in October 2023, and availability of Aβ-PET for clinical use has subsequently expanded significantly.

In January of 2025, a joint Alzheimer's Association–SNMMI workgroup published an updated set of Appropriate Use Criteria for amyloid PET, the first released since 2013[7]. The group evaluated the appropriateness of amyloid PET in 17 real-world clinical scenarios, and found that 7 were "appropriate", 2

"uncertain" and 8 "rarely appropriate". A summary of the AUC is shown in **Table 1**. The AUC also included appropriateness recommendations for Tau PET, which are beyond the scope of this Roadmap.

The "SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain 1.0" published in 2016 remains a vital summary of best practices regarding amyloid PET patient preparation, positioning, and imaging acquisition parameters. A summary is provided in **Table 2**. Aβ-PET may be performed as either PET/CT or PET/MR. The primary strengths of PET/CT are greater availability and shorter scan duration, benefits that may be especially relevant in patients who have already undergone recent high-quality MR imaging. Currently, the primary benefit of PET/MR for amyloid PET is patient convenience, allowing the simultaneous performance of two imaging studies which would otherwise be scheduled and conducted separately. In the future, PET/MR may offer improved diagnostic performance relative to PET/CT by allowing MR-guided PET reconstruction and advanced motion-correction techniques.[12]. In parallel, emerging CT- and MR-free approaches such as NeuroLF, which leverage deep learning to derive attenuation and anatomical information directly from PET data, may further expand access to amyloid PET quantification and simplify clinical workflows, although these methods remain under active investigation.[13]

Aβ-PET is interpreted first and foremost by visual read. In a normal study, cerebral radiotracer uptake is seen primarily within the white matter with sparing of the cerebral cortex, whereas in abnormal studies there is both nonspecific white matter uptake and pathologic uptake in the gray matter, resulting in blurring or loss of the normal gray-white contrast. The cerebellar cortex is typically spared even in advanced Alzheimer's disease and serves as a visual anchor/reference. While this fundamental principle holds true for all the amyloid radiotracers, the specific details are operationalized differently between FDA approved tracers, with discrepancies in factors such as whether the occipital lobes are considered and the number of abnormal regions required for positivity (**Table 3**). Representative clinical examples are shown in **Figure 1** (Florbetaben) and **Figure 2** (Florbetapir).

Within this framework, some centers employ a semi-quantitative visual approach to provide a structured assessment of amyloid burden in the cortex, namely the Brain Amyloid Plaque Load (BAPL) score[14]. In this paradigm, four cortical regions (frontal, parietal, lateral temporal, posterior cingulate/precuneus) are each graded by degree of radiotracer binding into three categories of Regional Cortical Tracer Uptake (RCTU); 1 = no cortical tracer binding, 2 = minor cortical binding, 3 = pronounced cortical binding. Aβ-PET scans with an RCTU score of 1 in each region are classified as BAPL 1, and considered to have no amyloid load. Scans with an RCTU of 2 in any or all regions but no regions receiving a score of 3 are classified as BAPL 2, generally considered as an equivocal or borderline case requiring additional review, quantification, or clinical correlation. Finally, scans with an RCTU of 3 in any region are classified as BAPL 3, confidently amyloid-positive and supportive of a diagnosis of Alzheimer's disease or other amyloid-associated conditions. Fundamentally, the assignment of regional RCTU scores remains a subjective exercise, and thus the derived BAPL scores are not a substitute for truly quantitative methods of amyloid PET analysis.

While visual interpretation, with or without semi-quantitative analysis, remains the gold standard for amyloid PET analysis, it has several important limitations. Many patients undergoing amyloid PET have cerebral atrophy, and the associated cortical thinning in combination with partial volume effects may produce an artifactual gray-white blurring, resulting in false positive cases. Conversely, in the absence of careful anatomic correlation, abnormal cortex and photopenic surrounding CSF spaces may be misinterpreted as normal white matter activity and preserved cortex, respectively, leading to false negative image interpretations. Further technical pitfalls which can complicate Aβ-PET interpretation include motion blurring and off-target uptake outside of the brain parenchyma. Finally, in the current era of anti-amyloid therapies, it is desirable to be able to reliably measure improvement in Aβ-PET over time. For all of these reasons, it is useful to supplement visual interpretation of PET with quantitative measures of amyloid burden.

4. Amyloid PET Quantitative Imaging Biomarkers

In daily clinical practice, Aβ PET studies are typically interpreted visually by radiologists who assess for Aβ tracer uptake in the cerebral cortex. However, visual interpretation can be prone to inter-reader variability, with disagreement rates of approximately 10-20%[15,16]. Therefore, quantitative tools have been developed to aid radiologists in providing more objective measures of Aβ deposition, which can be used to diagnose and monitor Aβ pathology longitudinally.

A commonly used metric in PET imaging is the standardized uptake value ratio (SUVR). The SUV in the targeted region is divided by the SUV in a reference region, which is typically chosen because it is not affected by the disease process. In the case of AD, the whole cerebellum, cerebellar gray matter, or the pons is often used. Studies that have used SUVR thresholds to determine Aβ positivity on PET have reported greater than 90% agreement[17,18], suggesting increased diagnostic accuracy compared to visual analysis alone.

Beyond a global SUVR threshold, many vendor software packages also offer the ability to compare a patient's PET SUVR with a normative database of healthy controls, resulting in a statistical Z-score. To do so, the software registers the patient's brain image to a common template space and segments the regions based on an atlas to obtain the SUVs. The Z-score represents the number of standard deviations that the patient's SUVR deviates from the mean of the reference group. Global, regional, and voxel-based Z-scores may be obtained[19-21]. Optimal Z-score thresholds for Aβ positivity have been reported to range from approximately 2 to 2.4, depending on whether the pons or cerebellar cortex is used as the reference region[22]. Regional z-score quantification derived from normative databases shows strong correlation with visual RCTU grading, supporting its feasibility as an objective adjunct to enhance diagnostic consistency and interpretation of amyloid PET[23].

While quantitative amyloid PET Z-scores show overall agreement across commercial platforms, region-specific and intermediate-burden variability may impact interpretation and treatment eligibility, underscoring the need for cross-platform standardization and validation[24]. Similarly, SUVR measures can vary by tracer, scanner type, image acquisition parameters, and image processing pipelines, including co-registration software and atlases used for segmentation[25]. Therefore, a direct comparison of SUVR values across studies, scanners, and institutions is difficult. Furthermore, for longitudinal follow-up, ensuring that a patient is imaged on the same scanner with the same parameters is logistically cumbersome.

Quantification by Centiloid values

Recently, the Centiloid (CL) project was proposed to develop a standardized, quantitative measure of Aβ deposition that could allow more accurate comparison of Aβ burden across imaging centers and tracers[26]. The approach uses an unbounded Centiloid scale anchored at 0 and 100, with zero representing the average Aβ burden of individuals with high certainty of being Aβ-negative. Alternatively, 100 represents the average Aβ burden of a typical patient with AD. Because the scale is unbounded, it is not limited to values of 0-100, however, and both negative values and values greater than 100 are possible. Data use to calibrate the CL thresholds for various Aβ-PET tracers are available on the Global Alzheimer's Association Interactive Network (GAAIN) website.[27]

Studies using CL values have typically used positivity thresholds around 24, with agreement between visual reads and quantitative thresholds for [F18] tracers ranging from 86-97%[28,29] . However, discordance remains in cases of low Aβ deposition, with scans in the 10-40 CL range more likely to be discordant. As a result, some studies have proposed two thresholds: one below which there is high certainty of the absence of Aβ pathology and one above which there is high certainty of the presence of Aβ on pathology[30-32]. For example, 10-13.5 CL have been proposed as the lower limit, below which the scan can effectively exclude early Aβ deposition. Conversely, 30-36 CL have been proposed as the threshold, above which there is likely pathological amounts of Aβ deposition. The intermediate range from approximately 14-30 would thus represent a borderline zone of people who are at increased risk of Aβ accumulation.

Although optimal thresholds remain a topic of investigation, the CL project sets the basis for more widespread standardization of Aβ-PET quantification. Having a standardized metric will be especially useful for longitudinal assessments, particularly those on anti-amyloid therapy, and for multicenter studies.

5. Software vendors currently offering Amyloid PET Quantification

Several Food and Drug Administration (FDA; 510[k])-cleared software tools are available for clinical implementation of the CL metric. These include cPET (Combinostics), MIMneuro (MIM Software), syngo.PET (Siemens), Hermia (Hermes Medical Solutions), and AQUA AD (Neurophet). At the time of this publication, integration of Centiloid is ongoing for the following software: NeuroQ (Syntermed) and Neuroquant PET (Cortechs.ai).[30] **Table 4** provides a summary of the software vendors presently offering amyloid PET quantification in the clinical setting.

Notably, in 2024, package inserts of the amyloid PET tracers were amended in the Europe Union to include quantification as an adjunct to the visual read.[33] This was followed by an update to the package inserts in the United States in late June 2025, which expanded the clinical indication for Aβ-PET to include use in both diagnostic assessment and identification of appropriate candidates for amyloid-targeting therapies. The update also endorsed the use of quantitative amyloid plaque metrics in conjunction with visual image interpretation, as well as broader use of Aβ-PET for monitoring of therapy and following progression to Alzheimer's disease[34].

6. Regulatory Considerations

In order to support FDA qualification of the CL metric as a biomarker for use across drug development programs, a formal FDA CDER Biomarker Qualification would be required. This would necessitate a well-defined Context of Use, along with a comprehensive analytical validation, including assessments of repeatability, bias, and traceability to a reference method orscale, as well as clinical validation packages.

To support a clinical decision-making use case, clinical validation would require the definition and pre-specification of cut points, such as Centiloid thresholds, with demonstrated robustness across tracers, scanners, demographics, and comorbidities. For applications involving tracking disease progression or treatment response, additional evidence would be needed, including test-retest reliability, longitudinal change characteristics, and alignment of the quantitative thresholds with underlying pathology consistent with the defined Context of Use.

If the metric is used to determine eligibility for therapy, it would likely be subject to imaging companion diagnostic scrutiny. This would require closer alignment between imaging labeling and drug indications, implementation of post-market performance monitoring, and controlled software updates in accordance with the FDA and IMDRF guidance for clinical evaluation of software as a medical device.

7. Reimbursement Considerations

Reimbursement for PET imaging scan is usually bundled and covers acquisition and interpretation, without separate reimbursement for quantitative analysis software. To influence payer coverage, evidence would be needed to demonstrate that quantitative metrics such as Centiloid values, meaningfully affect clinical management, for example, patient selection, treatment monitoring thresholds, improvement in inter-reader reliability, or reduction in repeat imaging. Subsequent steps could then involve engagement with professional societies to persue dedicated coding pathwats, such as Category III or add-on codes, or alternatively accepting bundled reimuursment, with but pricing structured accordingly for providers.

8. Clinical workflow considerations

The importance of quantifying amyloid PET measurements and their uncertainty have been highlighted in the Radiological Society of North America (RSNA) Quantitative Imaging Biomarkers Alliance (QIBA) profile[35]. Although this assessment focused on the SUVr measure, key points are also relevant to the CL metric.

Key clinical scenarios for the integration of the Centiloid scale in clinical practice[30] include (1) adjunct to visual assessments of amyloid-PET images to achieve high certainty regarding the presence or absence of Aβ pathology; (2) inclusion criterion for appropriate patient selection for anti-amyloid disease modifying therapies; (3) assessment for amyloid clearance following treatment with anti-amyloid disease-modifying therapies; (4) identification of early or emerging beta-amyloid pathology since Centiloid values in the indeterminate range are associated with increased risk of disease progression; and (5) support differential diagnosis in patients with co-pathologies and mixed dementia.

It is important to emphasize that the use of the Centiloid metric in the clinical setting should be implemented as an adjunct to, and not a replacement of, visual reads. Similarly to SUVr measures, Centiloid values depend on the quality of image acquisition and image processing, and may be inaccurate in patients with atypical amyloid distribution patterns, such as in cases with signal in cortical areas outside of the mask (e.g. occipital lobes) or in cases with elevated signal in the reference region (e.g. cerebellum)[30].

Finally, a key barrier to widespread implementation of Centiloid quantification in the clinical setting in the United States remains the lack of billing and coding guidelines for amyloid PET quantification. Therefore, reimbursement possibilities are uncertain at the present time, and further advocacy is needed in this arena.

9. Reproducibility across vendors

Reproducibility describes the agreement between measurements taken on the same subject but with different imaging methods (e.g. different vendors, analysis software, tracers)[36]. It is a critical component in a biomarker's technical performance capability, establishing the basis for the biomarker to diagnose, prognose, assess change over time, and in clinical trials for the biomarker to be used for patient selection and treatment monitoring.

The reproducibility coefficient (RDC) is a metric used to describe a biomarker's reproducibility. Differences between two serial measurements in the range of -RDC to +RDC are interpreted as differences expected due to measurement variability with some level of confidence (usually 95%), whereas differences outside the range might represent a biological change[37]. RDC is best measured in clinical test-retest studies.

Maximizing PET amyloid's reproducibility has been challenging due to inherent differences in tracers, scanners, post-injection acquisition times, reconstruction parameters, and image processing software[35,38]. The introduction of the Centiloid scale[26], however, has enhanced comparability of SUVr measurements. The scale has two anchors: 0CL for cognitively unimpaired people and 100CL for patients with typical-to-moderate AD. Centiloid values are expressed on a continuum between 0 and 100, with higher values representing more amyloid burden. SUVr values measured with different techniques are mapped to the scale using the appropriate formula[38].

Use of Centiloid values has led to enhanced reproducibility, with test-retest variability of ~ 3 Centiloid values[39]. Commercial software packages are increasingly reporting Centiloid values in their output, providing a pathway towards maximizing reproducibility.

10. EHR data transfer to radiology report

Data transfer to the electronic health record and reporting systems

In order to transmit results into an electronic medical record or other systems such as a reporting system, it is preferable to follow a standard methodology such as DICOM[40] or FHIR[41]. In addition, when the results are reviewed by a reporting physician (radiologist), it is desirable to have a standard method to audit those results and, if necessary, to change the result. These functions are already built into the IHE AI Results (AIR) profile[42]

and the AI Result Assessment for Imaging (AIRA) Profile[43]. While the algorithm used to calculate results may not necessarily use machine learning, these AI result workflows are well suited to report these results and provide auditing. Both of these profiles are currently in trial implementation[44].

Results format

To use the AIR profile, it is necessary to provide a codeset that defines the various measures used, such as SUVr and centiloid. Since these measures are currently not defined in a recognized codeset such as LOINC[45], it is proposed that a temporary codeset be used initially, with migration to LOINC in the future. This is the same approach used by IHE in the AIR results profile. This temporary codeset "99RSNAQUIC" has entries as summarized in **Table 5**.

To specify anatomic locations, existing SNOMET CT codes should be used[46]. For example, the cingulate gyrus is encoded in SNOMED CT as SCTID: 25221002.
Other details such as vendor, software version, and algorithm are specified as detailed in the AI Results profile.

Storage and transmittal
The AI Results profile creates a DICOM SR (structured report) object that can be stored along with the original images (which are also saved in DICOM). the DICOM SR can be mapped using the existing FHIR DICOM SR to FHIR Resource Mapping Implementation Guide for transmittal to an electronic medical record that relies on FHIR[47].

Auditing
The AI Result Assessment for Imaging (AIRA) Profile addresses the need to document and communicate the results from an assessment process. This profile can be used without additional specifications beyond what has been described thus far.

11. Relevant QIBA profiles

The technically confirmed QIBA Profile "18F-labeled PET tracers targeting Amyloid as an Imaging Biomarker"[35] published on documents technical specifications and requirements to provide comparability and consistency for the use of PET imaging using [F18] labeled amyloid tracers. The goal of a technically confirmed QIBA Profile is to help achieve a useful level of performance for a given biomarker. Quantitative measurement of amyloid has become increasingly used in clinical trials for patient inclusion, evaluation of disease progression, and assessment of treatment effects. This technically confirmed version of profile focuses on a longitudinal Claim, where the primary purpose is to assess change in amyloid load due to disease or following an intervention. In this case, precision is most important as long as bias remains constant over time. Characterization of measurement bias will be important for a cross-sectional claim wherein the amyloid tracer is used primarily to select amyloid positive subjects.

In a previous version of public comment QIBA profile[48], claim was made for brain amyloid burden as reflected by the SUVR is measurable from [F18] amyloid tracer PET with a within subject coefficient of variation of 2.9%. A measured change in SUVR of Δ % indicates that a true change has occurred if $\Delta > 8$ %, with 95% confidence. The Committee recognized that the threshold change metric (8%) cited in the Claim may not be practical or relevant for the assessment of biologic change or a modification of biologic change with a therapeutic intervention, since accumulation rates reported in the literature are on average from 1% to a few percent per year.

The **QIBA Amyloid PET Profile** ("18F-labeled PET tracers targeting amyloid as an imaging biomarker") provides standardized technical specifications to ensure comparability and consistency of amyloid PET quantification

across sites. The profile is *technically confirmed* and is designed primarily to support **longitudinal claims** – i.e., the reliable measurement of change in amyloid load over time, whether due to disease progression or therapeutic intervention.

- **Primary metric:** The standardized uptake value ratio (SUVR) was selected due to its feasibility across multicenter trials and its use in large reference studies such as ADNI.
- **Performance claim:** Sites conforming to the profile can achieve reproducible SUVR measurements with within-subject variability of ~2% when acquisition and analysis protocols are standardized.
- **Implications:** This level of precision improves statistical power for clinical trials, supports reliable subject selection, and strengthens longitudinal monitoring.
- **Limitations and future directions:** Current claims are based on relatively small short-term test–retest studies. Further validation over longer intervals and in diverse clinical contexts is needed to extend applicability to routine practice.

In summary, the QIBA Amyloid PET Profile lays the foundation for harmonized amyloid quantification, providing a benchmark for reproducibility that can be applied across academic, clinical, and industry settings

12. Interpreter qualifications

Amyloid PET scans should be interpreted by physicians with formal training in diagnostic imaging as well as specialized expertise in brain imaging. This includes familiarity with the full spectrum of dementia syndromes, recognition of normal aging versus pathological amyloid deposition, awareness of potential technical scan pitfalls, and the ability to integrate amyloid PET findings with information obtained from other neuroimaging modalities such as MRI or FDG PET. Qualified individuals would include board certified or board eligible nuclear medicine physicians, neuroradiologists, and other radiologists with documented training and demonstrated competency in molecular brain imaging[9].

Amyloid PET readers should also successfully complete the manufacturer-required reader training modules for each amyloid PET tracer used in their clinical practice. Completion of these modules and adherence to the reading methods described therein promotes consistent application of the interpretation criteria across different readers and institutions. Given the rapidly advancing field of neurodegenerative disease imaging, regular participation in additional professional society–endorsed training programs and related continuing medical education (CME) is strongly recommended. Such engagement reinforces technical proficiency and also promotes harmonization of reporting standards, ensuring that patients and referring clinicians receive imaging reports that are accurate and reflective of contemporary practice.

13. Implementation timeline

While amyloid PET quantification has matured substantially over recent years, its widespread clinical translation remains a work in progress. The path from validated research tool to routine clinical use involves multiple phases, each demanding coordinated efforts across stakeholders. A conceptual timeline (5–10 years) with major milestones and dependencies is presented in **Table 6**. In reality, these phases will overlap and feedback loops will be critical: lessons from early users should inform updates to standards and protocols, and implementation challenges should feed into future QUIC revisions.

A 2025 overview of Centiloid and amyloid PET quantification emphasizes that while the Centiloid transformation (introduced circa 2015) has enabled a common scale across tracers, more work is needed to bridge the gap from research to widespread clinical workflows (e.g. in reporting pipelines, automation, quality control)[38]. Meanwhile, Pemberton et al. note that although quantitative methods have shown promise in trials and retrospective analyses, further validation and broader adoption in clinical practice are needed to support therapeutic decision-making[49]. More recently, real-world data demonstrate that quantitative amyloid PET metrics,

including Centiloid and regional Z-scores, are sensitive to treatment-related amyloid clearance following anti-amyloid therapy and may correlate with cognitive outcomes, supporting their potential role in treatment monitoring[50].

To advance along this timeline, the QUIC Neurodegenerative Disease Group must proactively engage all relevant stakeholders:

- *Vendors and software developers:* to implement robust quantification pipelines, automate workflows, and commit to interoperability and standards.
- *Imaging centers / radiology groups:* to pilot implementation, provide feedback, and refine workflows.
- *Regulators & payers:* to recognize quantitative PET biomarkers as valid clinical tools and establish reimbursement frameworks.
- *Referring physicians (neurology, primary care):* to integrate quantitative readouts into diagnostic and therapeutic pathways.
- *Informatics / EHR / PACS teams:* to ensure seamless data transfer, result integration, and structured reporting.
- *Researchers / trial sponsors:* to generate the evidence linking quantitative change to clinical benefit, which is essential for regulatory and payer acceptance.
- *Patient & advocacy groups:* to foster awareness, patient consent pathways, and public acceptance of advanced imaging biomarkers.

14. Future goals for the QUIC Neurodegenerative Disease Group

The current roadmap represents an important step toward the standardization and clinical integration of amyloid PET quantification. However, the landscape of neurodegenerative disease imaging is rapidly evolving. To ensure continued relevance, the QUIC Neurodegenerative Disease Group has identified several areas of future work and expansion as outlined below.

Follow-up Survey on Implementation of Amyloid PET Quantification
Building on prior survey efforts, the group aims to conduct a follow-up survey to assess how amyloid PET quantification is being adopted in routine clinical practice. This will include:

- Use of quantification in diagnosis and differential diagnosis of dementia syndromes.
- Application in eligibility determination for anti-amyloid therapies.
- Variability in software platforms, workflows, and reporting practices across institutions.
- Barriers and facilitators to adoption, including reimbursement, training, and technical integration. This effort will provide benchmark data to guide ongoing quality improvement and education initiatives.

Amyloid PET Quantification in Treatment Response Assessment
As disease-modifying therapies become integrated into practice, there is an urgent need to determine whether amyloid PET quantification can serve as a reliable biomarker for monitoring therapeutic response. Goals include:

- Reviewing evidence from clinical trials that have used centiloid or SUVR change as endpoints.
- Establishing whether quantitative measures can guide treatment continuation or discontinuation decisions.
- Identifying the role of amyloid PET in post-marketing surveillance networks (e.g., ALZ-NET). Future QUIC work may involve consensus recommendations or a QIBA profile extension to support treatment monitoring applications.

FDOPA PET Quantification
FDOPA PET allows assessment of presynaptic dopaminergic function and is increasingly used in the evaluation of Parkinsonian syndromes. Quantification has the potential to:

- Standardize interpretation of striatal uptake asymmetry and regional loss patterns.
- Provide objective metrics for disease progression and response to therapy.

- Facilitate clinical trial enrollment and stratification in movement disorder studies. The group aims to explore harmonization of acquisition and analysis methods for FDOPA PET, building on lessons learned from amyloid PET standardization.

Flortaucipir PET Quantification
Quantitative tau PET is poised to transform the diagnosis and staging of Alzheimer's disease, with implications for both clinical practice and therapeutic monitoring. Future goals include:

- Reviewing evidence for SUVR- and centiloid-like standardization frameworks for Flortaucipir
- Assessing the role of tau PET quantification in disease staging, treatment eligibility, and tracking of disease-modifying therapy effects.
- Identifying technical and workflow challenges specific to tau PET (e.g., off-target binding, reference region selection).

Through these initiatives, the QUIC Neurodegenerative Disease Group will expand its scope from establishing amyloid PET quantification as a clinical standard to developing a comprehensive framework for quantitative neurodegenerative PET imaging biomarkers. This forward-looking agenda emphasizes longitudinal tracking, multi-tracer harmonization, and alignment with therapeutic advances, ensuring that the group's work remains central to the evolving practice of neuroimaging in dementia and movement disorders.

Figures.

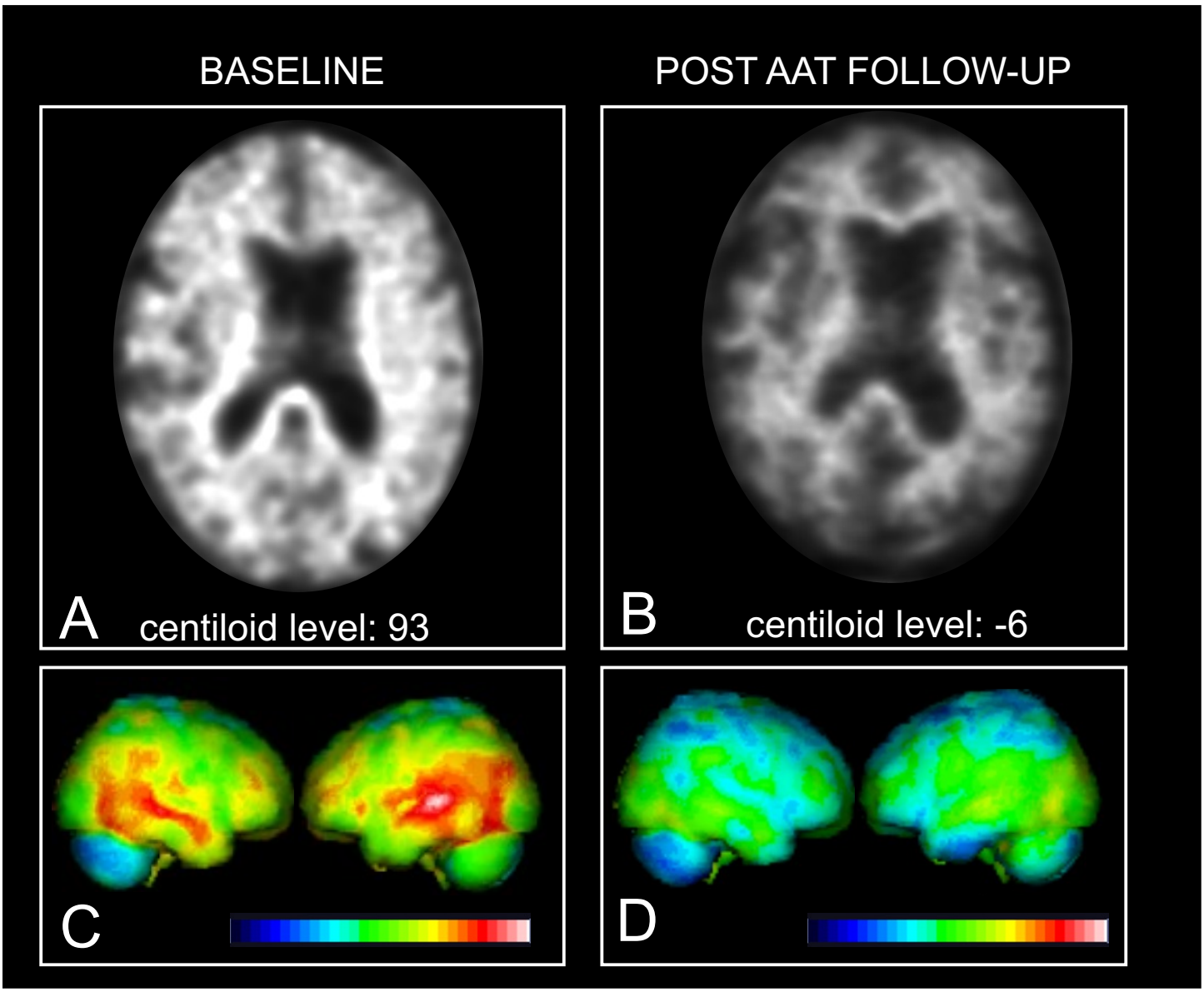

Figure 1. 82-year-old woman with MCI due to AD. Baseline Florbetaben PET shows diffuse cortical beta amyloid deposition (RCTU 3 in all regions, BAPL3, A). Centiloid analysis demonstrated a centiloid level of 93. Z-score analysis further confirmed elevation of supratentorial cortical region z-scores diffusely, most pronounced in the lateral temporal and inferior parietial lobes (C). Follow-up Florbetaben PET obtained after 19 months of anti-amyloid therapy (AAT) with Lecanemab demonstrates complete resolution of cortical radiotracer avidity (RCTU 1 in all regions, BAPL1, B), with a centiloid level of -6. Z-score analysis confirmed normalization of z-scores throughout all regions (D).

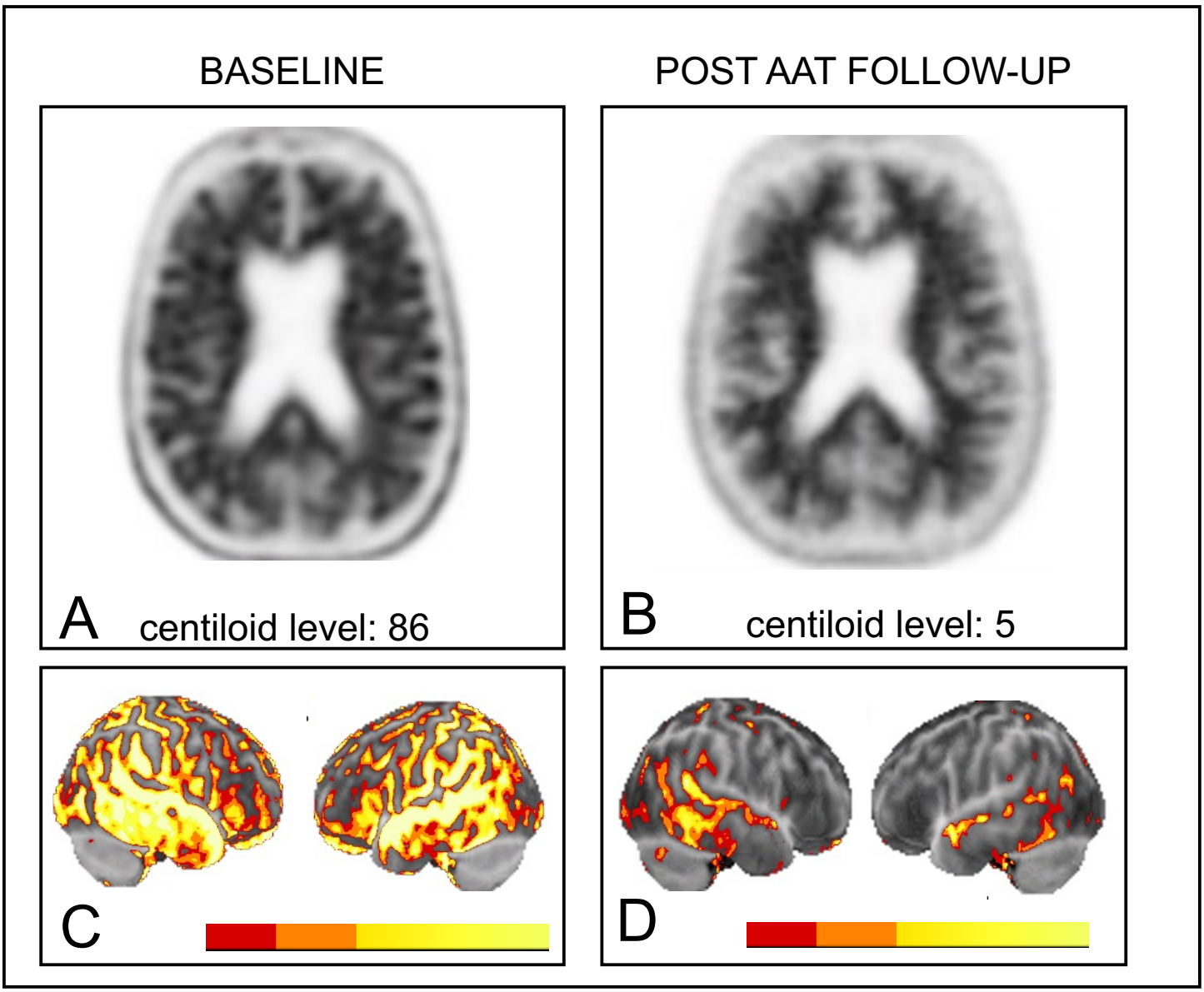

Figure 2. 78-year-old man with MCI due to AD. Baseline Florbetapir PET shows diffuse cortical beta amyloid deposition (RCTU 3 in all regions, BAPL3, A). Centiloid analysis demonstrates a centiloid level of 86. Z-score analysis further confirmed elevation of supratentorial cortical region z-scores diffusely, best visualized in the lateral temporal and inferior parietial lobes (C). Follow-up Florbetapir PET obtained after anti-amyloid therapy (AAT) demonstrates complete resolution of cortical radiotracer avidity (RCTU 1 in all regions, BAPL1, B), with a centiloid level of 5. Z-score analysis confirmed normalization of z-scores throughout all regions (D).

Tables.

APPROPRIATE
Patients presenting with MCI or dementia syndrome who are younger than 65 y and in whom AD pathology is suspected **(Rating 9)**
To determine eligibility for treatment with an approved amyloid-targeting therapy **(Rating 9)**
Patients presenting with MCI or dementia syndrome that is often consistent with AD pathology (amnestic presentation) with onset at 65 y or older **(Rating 8)**
Patients presenting with MCI or dementia syndrome that could be consistent with AD pathology but has atypical features (e.g., nonamnestic clinical presentation, rapid or slow progression, etiologically mixed presentation **(Rating 8)**
Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers **(Rating 8)**
To inform the prognosis of patients presenting with MCI due to clinically suspected AD pathology **(Rating 8)**
To monitor response among patients who have received an approved amyloid-targeting therapy **(Rating 8)**
UNCERTAIN
Patients with subjective cognitive decline (CU based on objective testing) who are considered to be at increased risk for AD based on age, known APOE4 genotype, or multigenerational family history **(Rating 6)**
To inform the prognosis of patients presenting with dementia due to clinically suspected AD pathology **(Rating 4)**
RARELY APPROPRIATE
Patients with MCI or dementia with recent CSF biomarker results that are conclusive (whether consistent or not consistent with underlying AD pathology) **(Rating 3)**
Patients who are CU but considered to be at increased risk for AD based on age, known APOE4 genotype, or multigenerational family history **(Rating 2)**
Patients with SCD (cognitively unimpaired based on objective testing) who are not considered to be at increased risk for AD based on age, known APOE4 genotype, or multigenerational family history **(Rating 2)**
Patients presenting with prodromal Lewy body disease or DLB **(Rating 2)**
Patients who are CU who are not considered to be at increased risk for AD based on age, known APOE4 genotype, or multigenerational family history **(Rating 1)**
To determine disease severity or track disease progression in patients with an established biomarker-supported diagnosis of MCI or dementia due to AD pathology **(Rating 1)**
Nonmedical usage (e.g., legal, insurance coverage, or employment screening) **(Rating 1)**
In lieu of genotyping for suspected autosomal dominant mutation carriers **(Rating 1)**

Table 1. AUC for Amyloid PET. A score of 1–3 is rarely appropriate, of 4–6 is uncertain, and of 7–9 is appropriate. Adapted from Rabinovici GD, et al. J Nucl Med. 2025;66(Suppl 2):S5–S31.

Tracer	Manufacturer	Injected Dose	Uptake Time (min)	Acquisition Duration	Recommended Color Scale / Reading Scheme	Quantification Notes (SUVR/ Centiloid)
[F18] Florbetaben	**Life Molecular Imaging**	**300 MBq (8.1 mCi) ± 20%**	45–130	10–20 min (static)	**Grey scale; PET Rainbow often used as adjunct**	**SUVR threshold typically 1.4–1.6**
[F18] Florbetapir	**Avid/ Eli Lilly**	**370 MBq (10 mCi) ± 20%**	**30-50**	**10 min (static)**	**Inverse grey scale (or recommended color scale referencing WM)**	**SUVR threshold 1.1**
[F18] Flutemetamol	**GE Healthcare**	**185 MBq (5 mCi) ± 20%**	**90**	**20 min (4 × 5 min frames)**		**SUVR threshold ~1.0**

Table 2. Summary of the three FDA-approved [F18]-labeled amyloid PET tracers and key imaging parameters. Values reflect manufacturer guidelines and published consensus recommendations. The final column highlights quantitative applications, including SUV ratio (SUVR) conventions and Centiloid conversion availability.

	Florbetapir	Florbetaben	Flutemetamol
Regions considered	**Cerebral Cortex**	**Temporal, Frontal, PCG /Precuneus, Parietal**	**Frontal, PCG/ Precuneus, Lateral Temporal, Inferolateral Parietal, Striatum**
Occipital lobe included	**Yes**	**No**	**No**
Number of regions required	**≥2 brain areas with reduced or absent GM-WM contrast or ≥1 area with intense cortical GM uptake > WM**	**≥1 of 4 defined regions with GM signal intensity ≥ WM, involving the majority of slices within the affected region.**	**≥1 of 5 defined regions with reduction or loss of GM-WM contrast**
Reference Region	**Cerebellum**	**Cerebellum**	**Cerebellum**

Table 3. Summary of the interpretation criteria for the three FDA-approved [F18]-labeled amyloid PET tracers. GM = gray matter, WM = white matter, PCG = posterior cingulate gyrus.

FDA 510(k) cleared
• cPET (Combinostics) • MIMneuro (MIM Software) • syngo.via PET (Siemens Healthineers) • Hermia (Hermes Medical Solutions) • AQUA AD plus (Neurophet)
FDA 510(k) clearance pending
• NeuroQ (Syntermed) • Neuroquant PET (Cortechs.ai)

Table 4. Centiloid (CL) quantification software currently available in the clinical setting.

Code	codeScheme	Code Meaning/ Definition
Centiloid	99RSNAQUIC	Centiloid level (global)
Z-score – ACG	99RSNAQUIC	Z-score, anterior cingulate gyrus region
Z-score – Frontal	99RSNAQUIC	Z-score, Frontal region
Z-score – Temporal	99RSNAQUIC	Z-score, Temporal region
Z-score – PCG	99RSNAQUIC	Z-score, posterior cingulate gyrus region
Z-score – Precuneus	99RSNAQUIC	Z-score, precuneus region
Z-score – Parietal	99RSNAQUIC	Z-score, parietal region

Table 5. Proposed temporary code set (99RSNAQUIC) for quantitative amyloid PET reporting. This table defines a provisional coding scheme for structured representation of quantitative amyloid PET metrics within DICOM SR and FHIR workflows. The code set includes a global Centiloid value and regional Z-scores (SUVr-based) for key cortical regions (anterior and posterior cingulate, precuneus, frontal, temporal, and parietal). Z-scores represent deviation from a normative reference dataset, expressed in standard deviations. These codes are intended for interim use until standardized terminology (e.g., LOINC) becomes available. Anatomic regions should be encoded separately using SNOMED CT concepts.

Phase	Time horizon	Key deliverables / activities	Dependencies & risks
Phase 0: Consolidation and harmonization	0 - 2 years	Finalization of cross-platform standardization (Centiloid adoption, vendor harmonization), publication of technical performance benchmarks, baseline surveys of current practice	Requires collaboration among vendors, QUIC, academic radiologists, and informaticists
Phase 1: Pilot clinical integration & early adopters	1 - 3 years	Integration in specialized centers (major clinical and research centers), structured reporting implementation, feedback loops, refinement of workflows	Needs vendor support, informatics integration, regulatory clarity, reimbursement models
Phase 2: Broad clinical adoption & reimbursement	3 - 5 years	Uptake across academic and community imaging centers, payer coverage policies, inclusion in clinical guidelines, expanded training and credentialing	Dependent on evidence generation (outcome correlation, cost-effectiveness), payer engagement, policy advocacy
Phase 3: Quantitative PET for treatment decision-making & response monitoring	5 - 10 years	Use of quantitative amyloid PET in therapeutic decision algorithms (initiation, escalation, discontinuation), longitudinal monitoring	Requires strong clinical trial data linking quantitative changes to outcome, regulatory and reimbursement pathways,

			integration with therapeutic frameworks

Table 6. Planned phases of the QUIC ND roadmap implementation.

References

1. Jack CR, Graf A, Burnham SC, et al. Application of the revised criteria for diagnosis and staging of Alzheimer's disease: Drug development and clinical practice. *Alzheimers Dement (N Y)*. 2024; 10(4):e70013.
2. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. *JAMA*. 2019; 321(13):1286-1294.
3. Windon CC, Gatsonis C, Carrillo MC, et al. Amyloid PET and clinical management in a diverse, cognitively impaired population: The New IDEAS Study. *Alzheimers Dement*. 2025; 21(7):e70504.
4. ALZ-NET: The Alzheimer's Network for Treatment and Diagnostics. https://www.alz-net.org/about-alz-net. Accessed September 7, 2025, 2025.
5. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis*. 2023; 10(3):362-377.
6. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med*. 2021; 384(18):1691-1704.
7. Rabinovici GD, Knopman DS, Arbizu J, et al. Updated appropriate use criteria for amyloid and tau PET: A report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup. *Alzheimers Dement*. 2025; 21(1):e14338.
8. Ivanidze J, Nordvig AS, Fajardo AR, Tsiouris AJ, Chiang GC, Osborne JR. Medicare Coverage of Amyloid PET: Implications for Clinical Practice. *AJNR Am J Neuroradiol*. 2023; 44(11):E45.
9. Ivanidze J, Franceschi AM, Wintermark M, et al. ASNR Consensus Statement: Integrating Neuro-PET Interpretation into Neuroradiology Training and Practice. *AJNR Am J Neuroradiol*. 2025.
10. Graham MM. The Future of Nuclear Medicine in the United States. *J Nucl Med*. 2023; 64(9):1352-1353.
11. Armstrong MJ, Gronseth GS, Day GS, Rheaume C, Alliance S, Mullins CD. Patient Stakeholder Versus Physician Preferences Regarding Amyloid PET Testing. *Alzheimer Dis Assoc Disord*. 2019; 33(3):246-253.
12. Khalighi MM, Young CB, Weiss S, et al. Enhancing the Diagnostic Accuracy of Amyloid PET: The Impact of MR-Guided PET Reconstruction. *medRxiv*. 2025.
13. Jehl M, Mikhaylova E, Treyer V, et al. Attenuation Correction Using Template PET Registration for Brain PET: A Proof-of-Concept Study. *J Imaging*. 2022; 9(1).
14. Barthel H, Gertz HJ, Dresel S, et al. Cerebral amyloid-beta PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. *Lancet Neurol*. 2011; 10(5):424-435.
15. Takenaka A, Nihashi T, Sakurai K, et al. Interrater agreement and variability in visual reading of [18F] flutemetamol PET images. *Ann Nucl Med*. 2025; 39(1):68-76.

16. Yamane T, Ishii K, Sakata M, et al. Inter-rater variability of visual interpretation and comparison with quantitative evaluation of (11)C-PiB PET amyloid images of the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) multicenter study. *Eur J Nucl Med Mol Imaging*. 2017; 44(5):850-857.

17. Bucci M, Savitcheva I, Farrar G, et al. A multisite analysis of the concordance between visual image interpretation and quantitative analysis of [(18)F]flutemetamol amyloid PET images. *Eur J Nucl Med Mol Imaging*. 2021; 48(7):2183-2199.

18. Pemberton HG, Buckley C, Battle M, et al. Software compatibility analysis for quantitative measures of [(18)F]flutemetamol amyloid PET burden in mild cognitive impairment. *EJNMMI Res*. 2023; 13(1):48.

19. Akamatsu G, Ikari Y, Ohnishi A, et al. Voxel-based statistical analysis and quantification of amyloid PET in the Japanese Alzheimer's disease neuroimaging initiative (J-ADNI) multi-center study. *EJNMMI Res*. 2019; 9(1):91.

20. Franceschi AM, Petrover DR, Giliberto L, Clouston SAP, Gordon ML. Semiquantitative Approach to Amyloid Positron Emission Tomography Interpretation in Clinical Practice. *World J Nucl Med*. 2023; 22(1):15-21.

21. Thurfjell L, Lilja J, Lundqvist R, et al. Automated quantification of 18F-flutemetamol PET activity for categorizing scans as negative or positive for brain amyloid: concordance with visual image reads. *J Nucl Med*. 2014; 55(10):1623-1628.

22. Lilja J, Thurfjell L, Sorensen J. Visualization and Quantification of 3-Dimensional Stereotactic Surface Projections for 18F-Flutemetamol PET Using Variable Depth. *J Nucl Med*. 2016; 57(7):1078-1083.

23. Yadav D, Knight-Greenfield A, Moirano J, et al. Amyloid PET Z-score Quantification and correlation with visual semiquantitative grading. *AJNR Am J Neuroradiol*. 2025.

24. Ebani EJ, Yadav D, Knight-Greenfield A, et al. Cross-Platform Concordance of Quantitative Amyloid PET Z-Scores in a Real-World Clinical Cohort of Patients with Cognitive Impairment and Suspected Alzheimer Disease. *AJNR Am J Neuroradiol*. 2026.

25. Schmidt ME, Chiao P, Klein G, et al. The influence of biological and technical factors on quantitative analysis of amyloid PET: Points to consider and recommendations for controlling variability in longitudinal data. *Alzheimers Dement*. 2015; 11(9):1050-1068.

26. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*. 2015; 11(1):1-15 e11-14.

27. Global Alzheimer's Association Interactive Network - Centiloid Project. https://www.gaain.org/centiloid-project Accessed 1/19/26.

28. Zeltzer E, Schonhaut DR, Mundada NS, et al. Concordance Between Amyloid-PET Quantification and Real-World Visual Reads. *JAMA Neurol*. 2025.

29. Khalafi M, Hojjati SH, Wang XH, et al. Concordance between Centiloid Quantification and Visual Interpretation of Amyloid PET Scans across the Alzheimer Disease Continuum. *AJNR Am J Neuroradiol*. 2025; 46(9):1884-1892.

30. Collij LE, Bollack A, La Joie R, et al. Centiloid recommendations for clinical context-of-use from the AMYPAD consortium. *Alzheimers Dement*. 2024; 20(12):9037-9048.

31. Bullich S, Roe-Vellve N, Marquie M, et al. Early detection of amyloid load using (18)F-florbetaben PET. *Alzheimers Res Ther*. 2021; 13(1):67.

32. Salvado G, Molinuevo JL, Brugulat-Serrat A, et al. Centiloid cut-off values for optimal agreement between PET and CSF core AD biomarkers. *Alzheimers Res Ther*. 2019; 11(1):27.

33. Agency EM. Centiloid measure of Amyloid PET to quantify brain amyloid deposition. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance/opinions-letters-support-qualification-novel-methodologies-medicine-development#centiloid-measure-of-amyloid-pet-to-quantify-brain-amyloid-deposition-66049. Accessed September 7, 2025.

34. FDA Grants Supplemental Indication Approvals to Three Amyloid PET Imaging Agents, Expanding the Role of Nuclear Medicine in Neurology. https://snmmi.org/Web/News/Articles/FDA-Grants-Supplemental-Indication-Approvals-to-Three-Amyloid-PET-Imaging-Agents--Expanding-the-Role.Mobile.aspx. Accessed September 7, 2025.

35. Smith AM, Obuchowski NA, Foster NL, et al. The RSNA QIBA Profile for Amyloid PET as an Imaging Biomarker for Cerebral Amyloid Quantification. *J Nucl Med*. 2023; 64(2):294-303.

36. Kessler LG, Barnhart HX, Buckler AJ, et al. The emerging science of quantitative imaging biomarkers terminology and definitions for scientific studies and regulatory submissions. *Stat Methods Med Res*. 2015; 24(1):9-26.

37. Pierce TT, Sirlin CB, Fowler KJ, Buckler AJ, Hall TJ, Obuchowski NA. Understanding Repeatability and Reproducibility Coefficients for Quantitative Imaging Biomarkers. *Radiology*. 2025; 316(2):e250279.

38. Iaccarino L, Burnham SC, Tunali I, et al. A practical overview of the use of amyloid-PET Centiloid values in clinical trials and research. *Neuroimage Clin*. 2025; 46:103765.

39. Shekari M, Vallez Garcia D, Collij LE, et al. Stress testing the Centiloid: Precision and variability of PET quantification of amyloid pathology. *Alzheimers Dement*. 2024; 20(8):5102-5113.

40. DICOM standard https://www.dicomstandard.org/. Accessed 1/19/26.

41. International H. FHIR https://www.hl7.org/implement/standards/product_brief.cfm?product_id=491. Accessed 1/19/26.

42. IHE. IHE Radiology Technical Framework Supplement https://www.ihe.net/uploadedFiles/Documents/Radiology/IHE_RAD_Suppl_AIR.pdf. Accessed 1/19/26.

43. IHE Radiology Technical Framework Supplement, AI Result Assessment for Imaging (AIRA) https://www.ihe.net/uploadedFiles/Documents/Radiology/IHE_RAD_Suppl_AIRA.pdf. Accessed 1/19/26.

44. IHE. Radiology (RAD) Domain https://profiles.ihe.net/RAD/index.html. Accessed 1/19/26.

45. LOINC https://loinc.org/. Accessed 2/24/26.

46. SNOMED https://www.snomed.org/. Accessed 2/24/26.

47. FHIR DICOM SR to FHIR Resource Mapping Implementation Guide. https://build.fhir.org/ig/HL7/dicom-sr/en/. Accessed 2/24/26.

48. Public Comment QIBA Profile. 18F-labeled PET tracers targeting Amyloid as an Imaging Biomarker. Available at. Accessed September 7, 2025.

49. Pemberton HG, Collij LE, Heeman F, et al. Quantification of amyloid PET for future clinical use: a state-of-the-art review. *Eur J Nucl Med Mol Imaging*. 2022; 49(10):3508-3528.

50. Ivanidze JG, J.; Olson, A.; Sun, S.M. ; Thomas. C. ; Wong, O. L.; Intorcia, B.; Moirano, J.; Tanavde, V.; Gershon, B.; Pahlajani, S.; Roytman, R.; Nordvig, A.; Lin, M.; Hamed, M.; Alport, A.; Salgado, M.; Keil, S.; O'Dwyer, E.; Lantos, J.; Huicochea Castellanos, S.; Ebani, E.J.; Agee, M.; Fink, M.E.; Osborne, J.R.; Chiang, G.C.; Blum, S. . PET-guided Assessment of Amyloid Clearance and

Outcomes in a Real-World Cohort of Patients with Alzheimer Disease undergoing Anti-Amyloid Therapy. *AJNR Am J Neuroradiol*. 2026 (in press)