Quantitative Brain Amyloid PET

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Since the development of amyloid tracers for PET imaging, there has been interest in quantifying amyloid burden in the brains of patients with Alzheimer disease. Quantitative amyloid PET imaging is poised to become a valuable approach in disease staging, theranostics, monitoring, and as an outcome measure for interventional studies. Yet, there are significant challenges and hurdles to overcome before it can be implemented into widespread clinical practice. On November 17, 2022, the U.S. Food and Drug Administration, Society of Nuclear Medicine and Molecular Imaging, and Medical Imaging and Technology Alliance cosponsored a public workshop comprising experts from academia, industry, and government agencies to discuss the role of quantitative brain amyloid PET imaging in staging, prognosis, and longitudinal assessment of Alzheimer disease. The workshop discussed a range of topics, including available radiopharmaceuticals for amyloid imaging; the methodology, metrics, and analytic validity of quantitative amyloid PET imaging; its use in disease staging, prognosis, and monitoring of progression; and challenges facing the field. This report provides a high-level summary of the presentations and the discussion.

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Alzheimer disease (AD) accounts for 50%–75% of people with dementia (*1*). It has overtaken cancer as America's most feared disease and is expected to become one of the most expensive diseases of this century (*2*). As a result, considerable efforts have been made to better understand the underlying pathophysiology and cognitive impairment of AD. AD is characterized by the accumulation of 2 proteins: plaques composed of amyloid-β and neurofibrillary tangles composed of pathologic aggregates of the microtubule protein tau. The amyloid hypothesis of AD proposes that amyloid-β accumulation is the initiating event in a cascade that occurs over a long period and eventually results in cognitive decline (*3*). Both amyloid-β and tau can be detected with PET scanning, cerebrospinal fluid assays, and, most recently, plasma assays. Therapeutic trials have focused on reducing both proteins in the brain in the hope of providing clinical benefit. Considering the early and crucial role of amyloid burden, determining and monitoring it in patients across the AD continuum is key to understanding AD. Amyloid PET allows for in vivo visualization, spatial localization, and quantitation of amyloid burden in the brain. Currently, 3 ^{18}F tracers are approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency for routine clinical use: ^{18}F-florbetapir,^{18}F-flutemetamol, and ^{18}F-florbetaben (*4–6*).

On November 17, 2022, the FDA, in partnership with the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Medical Imaging and Technology Alliance (MITA), cosponsored a public workshop to evaluate the role of quantitative PET measures of amyloid deposition in the brain and to identify critical gaps in knowledge. Clinical application of PET has largely used visual image interpretation. In this workshop, quantitative assessment generally referred to the use of SUV ratios (SUVRs) to provide a numeric measurement of tracer retention reflecting a continuum (as opposed to the presence or absence) of amyloid deposition. Representatives from academia, industry, and regulatory agencies participated in the workshop to address technical considerations of quantitative brain amyloid PET. The workshop comprised 4 sessions, with presentations followed by panel discussions. This report provides a high-level overview of key topics in the order they were presented and discussed during the workshop. Additional details and all workshop materials can be found on the public workshop webpage (*7*).

OPENING REMARKS

To open the workshop, Munir Ghesani, president of SNMMI, summarized SNMMI's goals for quantitative amyloid PET imaging. As part of its mission, SNMMI supports members with development of use criteria and educational materials for diagnostic radiopharmaceuticals to detect amyloid plaques in the brain. Ghesani noted that although PET scanners are often used to provide data for visual interpretation, they can measure radioactivity within a 5% margin of error. SNMMI understands that devices for quantitative amyloid PET are available and aims to help advance the technology.

Sue Bunning, industry director of PET for MITA, remarked on MITA's interest in amyloid PET imaging. MITA believes that medical imaging is a driver of effective patient care through screening, diagnosis, and treatment. MITA represents manufacturers of medical imaging equipment, radiopharmaceuticals, contrast agents,

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and focused ultrasound therapeutic devices. Members of MITA are interested in theranostics and therapies for many diseases, including AD, with the goal of helping patients obtain proper diagnoses and effective treatments.

To close out the introductory remarks, Alessandra Rovescalli, program director in the Clinical Interventions and Diagnostic Branch of the Division of Neuroscience at the National Institute of Aging (NIA), presented on NIA's efforts to support studies relating to amyloid PET imaging. NIA supported early efforts to develop ligands for amyloid detection, which resulted in the development of the first selective amyloid imaging compound, ^{11}C-Pittsburgh compound B. In 2004, NIA embraced the advent of the Alzheimer Disease Neuroimaging Initiative, which established a nationwide network of laboratories dedicated to neuroimaging in AD and is a key player in the advancement of AD biomarker research. Overall, NIA supports more than 30 AD research centers and a variety of investigator-initiated programs. Rovescalli closed the presentation with mention of the U.S. Health and Human Service's National Plan to effectively treat or prevent AD by 2025 (*8*).

SESSION I: QUANTITATIVE BRAIN AMYLOID PET IMAGING—BACKGROUND

Current State of Amyloid PET Imaging

William Jagust of the University of California, Berkeley, presented an overview of the current landscape of quantitative amyloid PET imaging, which has been used in research for staging, longitudinal observation, early detection, and prognosis. Clinically, however, quantitative PET has not yet been widely used, and brain amyloid PET images have been generally reported through visual interpretations of amyloid positivity or negativity. Jagust noted several challenges associated with quantitative amyloid PET that impede wider adoption, including establishment of consensus analysis methods standardized across tracers and scanners, establishment of robust and reliable thresholds to determine a positive versus negative scan, and techniques for assessing longitudinal change.

To facilitate discussion, Jagust provided a brief overview of the centiloid scale, which was developed to address standardization needs. This approach relies on a publicly available reference dataset from the Global Alzheimer Association Interactive Network repository using the amyloid imaging radiotracer ^{11}C-Pittsburgh compound B, which has been standardized to a scale from 0 (high certainty of amyloid-negative) to 100 (amyloid burden of a typical AD patient). By referencing additional tracers and processing methods to this dataset, any amyloid PET data can be transformed to this scale (*9*). The centiloid scale has now been used to establish thresholds for amyloid-positive status with similar sensitivity and specificity to histologic measurements obtained from autopsy for multiple tracers (*10–13*). However, thresholds do not always tell the whole story. In addition, because centiloids reflect a linear transformation from SUVRs, they maintain the disadvantages of this method. Many individuals who are below set thresholds accumulate amyloid, and accumulation in amyloid-negative individuals is associated with cognitive decline (*14–16*).

Although centiloids have helped to address the standardization problem, this scale could be dependent on the processing pipeline, and uncertainties remain over scalability and implementation as well as the effects of differences in instrumentation. There is also still uncertainty about whether centiloids provide enough precision to set numeric thresholds across multiple laboratories, whether measurements provide the precision necessary for longitudinal tracking of small changes, and whether the approach will scale for widespread adoption.

NOTEWORTHY

- Quantitation complements visual interpretation.
- Selection of brain reference region is important for quantitation.
- Simplification of quantitation is needed to encourage wider clinical use.
- Centiloids demonstrate a similar rate of amyloid accumulation across tracers of around 3–4 centiloids per year, showing the robustness of centiloids as a measure of longitudinal change.
- Ongoing developments include analysis methods, standardization across tracers and scanners, and reliable thresholds for amyloid burden at various stages of disease and for assessing disease progression.
- Standardized reference datasets and a uniform amyloid brain region atlas are needed for use across tracers and for software development.

Brain Amyloid PET: Overview of Clinical and Investigational Uses

Amyloid accumulation occurs slowly over decades before clinical symptoms of AD manifest, and current visual read methodology may lack the sensitivity to identify early amyloid deposition (*17*). The prolonged preclinical phase could provide an opportunity for early intervention before cognitive impairment. Quantitative amyloid PET imaging is likely the most important approach for detecting and monitoring early amyloid accumulation, Reisa Sperling from Massachusetts General Hospital explained. However, whereas amyloid accumulation is a hallmark of AD, it is not sufficient to predict the rate of subsequent cognitive decline (*18*). Of the known AD pathologies, tau neurofibrillary tangles have long been a primary determinant of cognitive decline in AD. Initial deposition of tau occurs focally in the medial temporal lobe and expands to the temporal neocortex, where its interactions with amyloid are posited to lead to neurodegeneration and cognitive decline (*19*,*20*).

Clinical trials have commonly used visual interpretation of amyloid PET imaging to identify amyloid-positive individuals, but this method may not be optimal, particularly if amyloid accumulation is not yet severe. For example, in the Anti-Amyloid Treatment in Asymptomatic AD study, only half of amyloid-positive individuals by quantitative assessment were classified as positive on visual reads, and 56% of amyloid-positive individuals in the tau PET substudy had already incurred substantial neocortical tau deposition (*21*). As a result, many clinical trials have targeted early intervention in at-risk individuals to prevent or delay the onset of cognitive impairment.

Characteristics of Brain Amyloid Tracers: Impact on Quantitation

Tracer selection for quantitative amyloid PET may impact image quantitation results, Victor Villemagne from the University of Pittsburgh explained. In patients with AD, the regional distribution of tracers in the brain is similar, but tissue ratios, dynamic ranges of values, pharmacokinetics, and optimal reference regions

for normalization or scaling differ (*9*). Additionally, differences in binding site affinities and proportions of binding sites across brain regions result in different tracer binding profiles in gray versus white matter (*22*). Tracers have high nonspecific retention in white matter, but amyloid plaques reside primarily in gray matter, so discrimination between the two and choice of reference region are important for quantitation.

Studies using centiloids demonstrate a similar rate of amyloid accumulation across tracers of around 3–4 centiloids per year (*15*,*17*,*23*) in all disease stages across the AD continuum, showing the robustness of centiloids as a measure of longitudinal change, independent of the tracer chosen. The centiloid scale has allowed researchers to begin to elucidate the natural history of amyloid accumulation in the brain and the impact of different factors such as age, sex, and apolipoprotein E ε4 status. For example, the rate of amyloid accumulation at early stages is faster in carriers of apolipoprotein E ε4 than in noncarriers (*24*), which could explain why the prevalence of high amyloid burden is greater in apolipoprotein E ε4 carriers (*25*). Establishing the natural history of AD may help guide interventional studies to establish optimal time windows for therapeutic interventions.

Panel Discussion

A panel of experts was gathered to opine on the current state of quantitative amyloid PET imaging. The panelists were Gil Rabinovici (University of California, San Francisco), Jonathan McConathy (SNMMI), and Phillip Kuo (University of Arizona, Tucson).

Visual Reads Versus Quantitation: Strengths and Weaknesses. Panelists agreed that visual reads and quantitation should be complementary. Visual reads are typically sufficient in patients with clinical impairment and can be useful for identifying focal areas of amyloid deposition that may fall below thresholds based on composite cortical measures (*26*). However, visual reads can be susceptible to reader bias, and 15%–20% of scans are difficult to judge (*26*). Together with visual reads, quantitation can increase confidence in diagnosis and help to clarify borderline cases. According to the panelists, quantitation has the potential to increase diagnostic accuracy and is essential for longitudinal follow-up when the human eye cannot reliably detect small changes in amyloid accumulation. However, there is heterogeneity in methods of quantitation and reconstruction of PET data, and diagnostic errors can occur. To enable wide implementation in clinical practice, the process of amyloid PET quantitation needs to be simplified with guidelines, parameters, and training.

Feasibility of Quantitative Amyloid PET Imaging in the Real World. In clinical practice, there are several options for tracers and scanners, as well as variable levels of expertise at imaging centers. Without standardized parameters for image acquisition and reconstruction, it may be difficult to implement quantitative amyloid PET imaging in clinics. However, studies suggest that quantitation of real-world clinically obtained data is feasible (*27*). The IDEAS study, which collected visual reads, also performed central analysis on real-world clinically obtained amyloid PET data to derive centiloid values without the use of MRI (*27*). There was high concordance between local clinical visual reads and amyloid positivity as defined by a threshold of 24 centiloids. This threshold may be clinically meaningful, as it detected intermediate to high levels of AD neuropathologic change in one clinical–pathologic correlation study (*12*) and moderate to frequent levels of plaque pathology in another study (*13*). It will be important to assess whether this approach is scalable and practical for obtaining standardized quantitative measures in clinical practice.

Scalability and Precision of the Centiloid Scale. The ability of the centiloid scale to detect clinically meaningful change in patients is unclear. Although large studies with substantial longitudinal follow-up may detect amyloid accumulation at a rate of approximately 3–4 centiloids per year at peak, limits of test–retest reliability make these measurements in individual patients over shorter observation periods challenging (*28*,*29*). Currently, this precision may not be necessary, since the major clinical uses are characterization of amyloid load in individuals and detection of amyloid decrease with treatment, both providing larger signals. However, should future disease monitoring become important, precise and scalable methods for longitudinal measurement will be required and are not yet available.

SESSION II: PRODUCTS FOR BRAIN AMYLOID IMAGING

Regulatory Perspectives on Technical Characteristics of Drugs for Brain Amyloid PET

Venkata Mattay, from the FDA, discussed development of diagnostic radiopharmaceuticals from a regulatory perspective. FDA's guidance for industry entitled, "Developing Medical Imaging Drug and Biologic Products Part 2: Clinical Indications" (June 2004) outlines 4 general categories of indications for medical imaging products, of which amyloid tracers fall into the category of disease or pathology detection or assessment (*30*). The effectiveness of radiopharmaceuticals is determined through evaluation of the agent's ability to provide useful, accurate clinical information related to the indication. Accuracy and validity are established through comparison of the diagnostic imaging agent with a truth standard (presence or absence of amyloid pathology by neuropathologic examination) and evaluation of the reproducibility of image interpretation. Using these standards, FDA has approved 3 ^{18}F tracers for assessing cerebral amyloid plaque pathology in the diagnostic work-up of suspected AD, all with similar scanning protocols and different visual rating protocols (*4–6*). Currently, the tracers are approved only for diagnostic work-up based on visual interpretation of the presence of amyloid and are not approved to make a clinical diagnosis of AD. Quantitative metrics with these tracers are now being used in natural history studies for detection of early amyloid deposition, AD staging and monitoring disease progression (*17*,*31–34*).

Regulatory Perspectives on Devices for Brain Amyloid PET Quantitation

Regulatory considerations for devices for quantitation of amyloid PET imaging were outlined by Daniel Krainak, from the Center for Devices and Radiologic Health at the FDA. There are 2 types of devices necessary for quantitation of amyloid PET: PET scanners and analysis software. Most devices on the market are cleared through the 510(k) premarket notification pathway that requires sponsors to demonstrate substantial equivalence to a predicate device (*35*), which is adjudicated on intended use and performance data. Devices must have the same intended use, and differences in technical characteristics cannot raise questions about safety and effectiveness compared with the predicate device. If the 510(k) pathway is not appropriate, devices may be submitted for premarket approval, which generally requires a greater body of evidence to provide reasonable assurance of safety and effectiveness.

Image software can be used for qualitative and quantitative purposes. Qualitatively, software tools assist physicians in classifying

images as either amyloid-positive or amyloid-negative. Quantitative software measures some objective characteristic from an image on a ratio or interval scale (e.g., SUVRs derived from comparison of average intensity in one region of the brain to another). Theoretically, any software with SUVR capabilities could be used for quantitative amyloid analysis. With any quantitative measurement, there are inherent uncertainties. Labeling for devices should communicate uncertainty associated with metrics or primary sources of variability if quantitative imaging functions are not able to provide specific performance metrics for uncertainty. FDA's recent guidance for industry entitled, "Technical Performance Assessment of Quantitative Imaging in Radiologic Device Premarket Submissions" (June 2022) provides guidelines for software and outlines information recommended for premarket submission of radiologic devices (*36*).

Amyloid Quantitation Methodologies

Binary assessment of whole brain amyloid status is often sufficient in clinical practice. However, continuous measures are critical for detection of intermediate amyloid accumulation, studies of natural history, and measurement of longitudinal change. This is particularly important since individuals who are nominally amyloid-negative may nevertheless have amyloid levels in the high reference range and are accumulating amyloid and at risk of cognitive decline. Susan Landau from the Helen Wills Neuroscience Institute at University of California, Berkeley, discussed the effects of image acquisition/reconstruction (e.g., injected dose and acquisition time) and processing/analysis (e.g., regions of interest and image resolution) on quantitation of amyloid. For longitudinal analysis in particular, stability of these factors and selection of reference regions of interest are key issues.

Test–retest reliability assessments can help to elucidate sources of technical variability. Several studies evaluating test–retest reliability using numerous sample sizes and methods have converged on an approximately 5% range in variability in scan duration on SUVRs (*37–39*), effects of smoothing (*40*), and differences in centiloid pipeline (*11*). Additionally, centiloids can account for the effects of acquisition/processing, enabling standardization across heterogeneous datasets (*41*). Crucially, centiloid standardization must use the Global Alzheimer Association Interactive Network dataset to replicate the original pipeline and assess a new pipeline (*9*).

Landau highlighted several unsolved problems with amyloid quantitation. First, most current processing pipelines are not fully automated and require expertise and adequate training to use properly. Second, though most thresholds for amyloid positivity converge on approximately 20 centiloids, there is still variability in thresholds used (*27*,*41–43*). Third, there is a lack of consensus on how to deal with the intermediate centiloid range, which represents a population of patients who are likely to become amyloid-positive subsequently. Finally, longitudinal change is more vulnerable to pipeline variability and processing factors that are difficult to validate without a reference standard (*41*,*44*).

Panel Discussion

Clinician and software developer panel members discussed the challenges facing quantitative amyloid PET in clinical practice. Panel members included C. David Cooke (Syntermed), Johan Lilja (Hermes Medical), Satoshi Minoshima (University of Utah), Jon Piper (MIM Software, Inc), and Marcus Steward (Siemens Medical Solutions).

Challenges in Advancing Quantitative Amyloid Analysis into Clinical Practice. Standardization of pipelines and reference datasets is needed for clinicians to obtain the same values regardless of software package, scanner, or pipeline used. As new scanners are developed, software developers need data from the scanners to develop reference files for use with that scanner and software pairing; however, competing companies may not be willing to provide the necessary scans to competitors, and obtaining new reference patient datasets is challenging. The panelists emphasized the need for a uniform amyloid brain region atlas for use across tracers, integration of software into routine clinical workflows, training and education programs, data sharing, and standardized reference datasets.

Labeling Considerations for Devices and Radiopharmaceuticals. Since the time of the approval of currently marketed amyloid PET tracers, advances in technology have led to a rapid pace of development and marketing of novel PET imaging devices such as scanners and software. Some of this marketed software is labeled with amyloid PET interpretation techniques that are not reflected in the current prescribing information for approved amyloid PET drugs. The panel suggested that labeling of amyloid PET imaging devices and drugs should aim to achieve greater consistency to aid clinicians in image interpretation as new technologies are developed and implemented in clinical practice.

SESSION III: QUANTITATIVE BRAIN AMYLOID PET IMAGING METHODOLOGY, METRICS, AND ANALYTIC VALIDITY

Semiquantitative and Quantitative Metrics

Julie Price from Massachusetts General Hospital provided an overview of the methodology, metrics, and analytic validity of PET imaging. There are many methods for quantifying amyloid PET. Fully quantitative pharmacokinetic compartmental modeling can provide data on radiotracer delivery (reflective of blood flow) and radiotracer-specific binding that may also reflect atrophy; however, this type of analysis is not feasible for clinical application because of the need for arterial blood samples and the long imaging durations (i.e., beginning at time of injection). Similarly, the use of other methods such as the Simplified Reference Tissue Model and Regression Methods also require long scan times. Therefore, late-scan SUVR is most often applied because it requires a shorter, static scan, though kinetics in the reference region and tissue and plasma clearance can impact its accuracy. Regardless of method chosen, the outcome measure should not be dependent on blood flow, should be stable over the chosen time interval, and should have acceptable reproducibility. Price emphasized that all methodologies involve a compromise among accuracy, precision, and study feasibility (*45–51*).

Every method relies on basic assumptions, and it is important to consider how the in vivo kinetics of the selected tracer satisfy the underlying assumptions. SUVR is a surrogate measure of radiotracer volume of distribution at equilibrium, but amyloid radiotracers are cleared from the brain during studies, leading to bias in SUVR. If steady state is established and clearance occurs at a constant rate, this bias can be accepted, particularly for amyloid load levels observed for the cognitively unimpaired (*52*,*53*). There is also a concern that amyloid tracers could be sensitive to differences in blood flow due to different rates of cerebral atrophy between the target and reference tissue, which might make SUVR measurements more vulnerable to bias. However, optimal SUVR time windows have been suggested to mitigate bias (*53*), and the

biasing effect of relative cerebral blood flow on SUVR appears limited in a cohort rich with the cognitively unimpaired (*52*).

Price closed by emphasizing differences across radiotracers, such as dynamic range and degree of cortical retention, that impact the ability to compare data from different studies and that need to be considered when trying to detect early disease and measure longitudinal change. Regardless of which radiotracer is used, persistent quantitation issues include reference region selection, motion, scanner differences, partial-volume correction, and reproducibility. These issues may all impact SUVR tissue ratios and centiloid values, and there are ongoing efforts to reduce these sources of variability.

Variability in Quantitative Brain Amyloid PET Metrics

Juan Domingo Gispert from the Barcelonaβeta Brain Research Center and Universitat Pompeu Fabra provided details about variability in quantitative amyloid PET metrics in the context of the Amyloid Imaging to Prevent Alzheimer Disease study (*54*,*55*). Centiloid scaling is applied to render a harmonized metric of amyloid load using SUVR measures from different scanners, tracers, reference regions, and quantitation pipelines (*9*). Centiloids can be used for assessing the level of amyloid neuropathology, evaluating disease progression, and determining clinical trial eligibility (*29*). They also have prognostic value, in that a range of centiloids is predictive of cognitive decline in cognitively normal individuals (*56*).

Gispert discussed the importance of quantifying variability associated with different sources of bias and uncertainty, such as processing pipelines, on centiloid values. To this end, ^{18}F-flutemetamol and ^{18}F-florbetaben scans from 330 participants of the Amyloid Imaging to Prevent Alzheimer Disease Diagnostic and Patient Management study (*57*) were processed with 32 centiloid-calibrated pipelines using combinations of reference regions, reference and target region types, and coordinate spaces. Bias associated with the sources of variability were estimated using a repeated-measures model. Within-pipeline analyses found bias to be below the test–retest variability with low uncertainty, except for the use of the pons as a reference region, which resulted in a centiloid value above the test–retest threshold. Additional analyses showed minimal impact of effective image resolution, and between-pipeline comparisons demonstrated good agreement between measurements (*58*).

Outside the centiloid model, other amyloid metrics have their own pros and cons. Kinetic modeling with nondisplaceable binding potential and distribution volume ratios moderately improve accuracy, precision, and robustness to technical confounders and physiologic confounders compared with SUVRs and centiloids (*52*,*59*–*61*). However, such dynamic measurements require more scanning time, result in greater participant burden, and cannot be compared across tracers. Other ratio-based metrics, such as *z* scores, show good correlation to centiloids, but the units are not based on publicly available reference groups (*62*,*63*). Thus, despite limitations, centiloids are a robust and useful method to render metrics of amyloid burden that are comparable across quantification methods and tracers.

Panel Discussion

Roger Gunn (Invicro and Imperial College London), Victor Villemagne (University of Pittsburgh), Julie Price (Massachusetts General Hospital), and Juan Domingo Gispert (Barcelonaβeta Brain Research Center/Universitat Pompeu Fabra) discussed quantitative brain amyloid PET imaging methodology, metrics, and analytic validity.

Numerous image acquisition factors in addition to scanner type impact quantitative amyloid PET modeling (e.g., tracer) and add complexity. Artificial intelligence has potential utility when there is no model or when other modeling approaches fail to address the complexity due to the multifactorial nature of the problem. For example, artificial intelligence could assist in defining the best regions for early amyloid detection.

Dealing with uncertainty in neurology is not dissimilar from treating other disease states; blood pressure, glucose, and hemoglobin A1c measurements are all continuous measures like centiloids. Therefore, there needs to be a range of centiloid measurements for which there is high confidence a scan is negative, high confidence it is positive, and an intermediate range. Regarding the latter, there may be multiple ways to use intermediate results. For example, patients in the intermediate range may be asked to repeat the scan in 2–3 y.

Interpretation of information depends on sensitivity and specificity and how best to balance these metrics. Quantitative data add to a physician's decision making because a binary result is not always adequate. How the data will impact decision making is likely dependent on the purpose for obtaining an amyloid PET scan and the clinical decision being made. Studies have shown that when clinicians were presented with amyloid images with quantitative data, changes in patient management were more frequent with positive scans, and changes in diagnosis were more frequent with negative scans (*26*). A key point is that amyloid deposition is a continuous risk factor, like cholesterol, and quantitation could help to determine a proper course of treatment.

SESSION IV: QUANTITATIVE IMAGING IN STAGING OF DISEASE, PROGNOSIS, AND MONITORING DISEASE PROGRESSION—IMPLICATIONS FOR DIAGNOSTIC IMAGING DRUG LABELING

Evaluation of Qualitative and Quantitative Imaging: Implications for Diagnostic Imaging Drug Labeling

Sue-Jane Wang from the FDA discussed considerations for medical imaging drug development programs. All 3 FDA-approved amyloid PET tracers are indicated for use in adult patients with cognitive impairment being evaluated for neurodegenerative diseases (*4*–*6*). The development programs for the approved tracers shared 3 key characteristics: comparison to a truth standard, determination of reliability through intra- and interrater agreement, and evaluation of diagnostic performance (sensitivity and specificity). Readers for the development programs had undergone specific image training to interpret the scans for the presence or absence of amyloid (i.e., positive vs. negative test). Labeling states that efficacy for predicting development of AD, dementia, and other neurologic condition or for monitoring response to therapy has not been established (*4*–*6*). More recent data indicate there is potential clinical utility in quantitative amyloid PET for disease staging, prognosis, and monitoring of progression (*17*,*31*–*34*). However, it is important to gain more regulatory experience to improve the understanding of quantitative amyloid PET for these uses.

The population of interest for drug development is often patients in the early phases of the AD continuum (*64*). However, there is significant uncertainty associated with this population, including lack of a truth standard (autopsy is too distant from the preclinical phase of the AD continuum) and the consequences of uncertain visual read reliability (*21*).

Studies designed to assess the clinical utility of quantitative amyloid PET would need to address measurement error, systematic bias, and variability. Key considerations in trial design include standardization of scan technique, image interpretation, reporting, and

progression criteria. For studies focused on prognosis, performance demonstrated against a prespecified threshold for a clinical outcome at a landmark time may serve as the truth standard. For monitoring of longitudinal change or disease progression, studies should compare baseline imaging with serial imaging to evaluate the pattern of change in amyloid imaging and its association with disease outcome.

Academic and Industry Perspectives on Brain Amyloid PET

Mayo Clinic. Val Lowe from the College of Medicine, Rochester, Minnesota, discussed efforts by the Mayo Clinic to define the natural history of AD. The Mayo Clinic Study of Aging is an ongoing population-based study in which subjects are monitored for AD development with an aim to describe early AD pathology. The group found that quantitative amyloid PET with SUVR from Pittsburgh compound B PET correlates with neuropathologic scoring methods (e.g., neuritic plaque score) (*65*). However, high amyloid burden does not necessarily mean a patient is on track to develop AD (e.g., many patients with high SUVR and frequent diffuse plaques do not have neuritic plaques), indicating that there are other contributing factors, such as regionality of amyloid. Quantitative amyloid PET can also aid in understanding mixed pathology by allowing clinicians to resolve subtle increments of amyloid deposition. In cognitively normal subjects, regional hypometabolism is associated with regional amyloid, following a dose–response relationship that can be quantified with amyloid PET (*66*). These quantitative data can assist development of data-driven models of AD pathology.

Another contributing factor to early AD pathology may be tau. Although amyloid is typically thought of as the early AD marker, tau accumulation leads to cognitive impairment (*67*). Changes in tau PET imaging occur with and without amyloid-positive scans in the cognitively normal population, and widespread diffuse tau deposition can sometimes be seen in the brain even without amyloid, earlier than previously thought (*67*). The future of the overarching Mayo Clinic Study of Aging seeks to further characterize AD pathology and to determine the association between contributing etiologies seen in preclinical stages and in clinical syndromes.

European Labeling Experience. The European Medicines Agency has amended the labeling for the 3 approved amyloid PET tracers to include quantitation to supplement visual image interpretation. Gill Farrar of GE Healthcare summarized the different approaches used by the development programs to support the labeling changes as well as general considerations that arose from the experience. Although the approaches for the 3 tracers differed, the programs all assessed concordance between visual and quantitative reads, compared with a truth standard, and used Conformité Européenne–marked software that is in compliance with all European requirements regarding safety, health, and environmental and consumer protection. Results from the programs found improved accuracy when combined with quantitation in less experienced readers and strong concordance between visual and quantitative reads (*68*,*69*). Findings also support the idea that quantitation and visual inspection methodology are complementary, and both contribute to overall image interpretation. The labeling for amyloid tracers includes language specifying that quantitation is for adjunctive use for image interpretation to improve reader accuracy, that readers must be trained on Conformité Européenne–marked software and visually interpret scans before quantitation, and that quality checks of the process are required (*70*–*72*).

Early Detection of Amyloid and Prognosis. Andrew Stephens of Life Molecular Imaging discussed the value of amyloid quantitation and the value of the centiloid scale on early detection and prognosis for AD. AD pathology is characterized by sequential trajectories of amyloid plaques, neuroinflammation, and tau accumulation; the latter is most closely linked to loss of neuronal function and cognitive decline (*73*). Though there are some uncertainties with amyloid quantitation and centiloid pipelines, they are generally robust overall. In data from a phase 2 study assessing ^{18}F-florbetaben image reads with 15 different software packages, concordance between visual read and quantitative read was 100% at high and low amyloid levels but dropped off in the intermediate levels (*63*). The amount of amyloid is predictive of progression, with moderate to high levels progressing most quickly (*34*). Quantitation can help distinguish the intermediate level of amyloid accumulation and determine progression, both of which are important for identification of early AD and study of possible interventions.

Quantitative Amyloid and Tau in Clinical Research. Mark A. Mintun of Avid Radiopharmaceuticals and Eli Lilly and Co. presented on the value of quantitative amyloid and tau PET imaging in clinical research. Quantitation may be particularly valuable in improving sensitivity in preclinical populations when a significant number of subjects may meet quantitative criteria but are amyloid-negative by visual read. For clinical trials, quantitation can help to set a threshold for inclusion criteria (*74*). Amyloid imaging appears critical for accurate prognosis and management of patients with AD, but one of the key difficulties in trials of AD is variability in how amyloid behaves over time and the ability to predict progression. Though amyloid appears to contribute to cognitive decline, tau is more strongly associated with it (*75*). However, tau has more heterogeneity in spread than amyloid, and in cross-sectional comparisons of subjects evaluated for diagnosis verification, it appears to decrease with advanced age (*69*,*76*). Consequently, the field is coming to consensus on harmonization of measurement of tau PET. Overcoming challenges with tau quantitative imaging will be important for broad use in disease diagnosis, progression, and management. Overall, both amyloid and tau quantitation are valuable and needed for clinical use.

Panel Discussion

The session IV panel consisted of Tammie Benzinger (Washington University), Gregory Klein (Roche), Jonathan McConathy (SNMMI), Stephen Salloway (Brown University), and Reisa Sperling (Massachusetts General Hospital), who convened to discuss the industry and academic perspectives on amyloid quantitation.

Quantitative Definition of Amyloid-Positive in Staging of Disease. Panelists posited that a one-size-fits-all approach to an amyloid-positive threshold would not be appropriate for all disease stages because of the variability of AD. A patient with dementia would have a different cutoff than an asymptomatic patient, and some individuals with high amyloid are cognitively normal whereas others with low amyloid are cognitively impaired. It is important also to consider other aspects of disease beyond amyloid burden such as cognitive state, apolipoprotein E ε4 status, and tau levels. Panelists were more comfortable with a threshold for amyloid-negative (e.g., $<$10 centiloids). Staging is a continuum, and thresholds are useful in defining confidence in the amount of amyloid plaque and risk of progression. To improve the quantitative scale, a study that defines meaningful clinical outcomes is necessary.

Truth Standard for Diagnostic Imaging Drug Development. A major issue with imaging drug development for early AD is the lack of a truth standard for comparison. Panel members mused on the risk of progression as a potential reference standard. There are clinical data to determine what the risk is, though work may be

required to harmonize across datasets. To satisfy regulatory standards and prevent bias, identifying a prespecified threshold is necessary. Ideally, the data would allow clinicians to make assessments based on centiloid values and patient demographics. Both amyloid and tau data will likely be needed.

CONCLUSION

Significant progress has been made over the past decade in understanding AD. Amyloid PET imaging has allowed clinicians to visualize the amyloid burden in patients and is now poised to assist further in disease staging, progression, and management through quantitation. Quantitative methods for amyloid burden, such as the centiloid scale, are sufficiently advanced to address some of the challenges related to implementation and interpretation. The outstanding challenges include control of variability within sites and across sites over time, including harmonizing image acquisition and ensuring clinicians appropriately integrate quantitative information into patient evaluation and management. Potential opportunities for quantitative amyloid imaging include advancing the understanding of risk of progression, demonstrating the value in cases with challenging qualitative interpretation, and categorization of cases beyond positive or negative (e.g., low, intermediate, or high). Efforts are needed to develop and consolidate standardized image processing pipelines and provide resources for training clinicians to correctly interpret quantitative amyloid information.

2023 POSTMEETING UPDATE

Since the workshop was held in November 2022, the results of trials of antiamyloid therapies that included quantitative assessment of amyloid PET burden have been published and demonstrate the use of the technology for drug development. In addition, the study results suggest the potential utility of quantitative PET amyloid imaging in new contexts of use, such as monitoring response to therapy.

Van Dyck et al. (*77*) published the results of a therapeutic study on subjects with mild cognitive impairment or mild dementia due to AD and evidence of amyloid either by amyloid PET based on visual interpretation recommended in the labeling of the 3 approved PET drugs or by cerebrospinal fluid amyloid-β 1–42. In a substudy assessing response to treatment, amyloid-β plaque levels in the brain by PET using both the SUVR and the centiloid scale decreased in subjects receiving the active drug compared with subjects in the placebo group.

Sims et al. (*78*) reported a therapeutic study of subjects with early symptomatic AD (mild cognitive impairment or mild dementia) and a positive amyloid PET scan defined by a centiloid threshold. Subjects were also triaged using a tau PET scan and categorized as either low/medium tau or high tau. The centiloid unit was also used to monitor the treatment response and to switch subjects to a placebo when a specified decrease in centiloid units was observed. At the end of treatment, there was a decrease in amyloid burden in the active arm relative to a negligible change in the placebo group.

In July 2023, the NIA–Alzheimer Association drafted revisions to the clinical criteria for AD and began seeking public comments (*79*). The new guidance defines neurodegenerative diseases based on biologic status as opposed to syndromic presentation. The framework also aims to categorize in vitro testing and imaging into core AD and noncore biomarkers and articulates the potential use cases (diagnosis, staging, prognosis, assessment of treatment effect, identification of copathology) and whether these assessments are for initial, early, intermediate, or advanced staging.

Updating of appropriate use criteria for amyloid and tau PET imaging is ongoing. The new criteria highlight the potential value of amyloid imaging in patients presenting with both mild cognitive impairment and dementia due to suspected AD; the criteria might be applicable to any age group and to both typical and atypical clinical presentations. Other uses under study are for therapy initiation, evaluation of clinical prognosis, and use when a cerebrospinal fluid measure is equivocal.

Additionally in 2023, the Quantitative Imaging Biomarkers Alliance developed a profile for assessment of the longitudinal changes in amyloid load and reported that within-subject variability in an SUVR measure at any site from technical factors can be limited if the site conforms with consistent calibration, acquisition, and reconstruction procedures (*80*). This paper is particularly relevant to support the technical discussion in this review article.

In summary, recent developments highlight the potential value of quantitative amyloid PET, although there are areas that need further clarification. Quantitative metrics such as the centiloid scale have been used in the recruitment of trial subjects and to monitor the activity of antiamyloid therapies and need further study and standardization.

DISCLOSURE

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