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REVIEW ARTICLE

The ADNI PET Core at 20

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Abstract

The Alzheimer's Disease Neuroimaging Initiative (ADNI) PET Core has evolved over time, beginning with positron emission tomography (PET) imaging of a subsample of participants with [^{18}F]fluorodeoxyglucose (FDG)-PET, adding tracers for measurement of β-amyloid, followed by tau tracers. This review examines the evolution of the ADNI PET Core, the novel aspects of PET imaging in each stage of ADNI, and gives an accounting of PET images available in the ADNI database. The ADNI PET Core has been and continues to be a rich resource that provides quantitative PET data and pre-processed PET images to the scientific community, allowing interrogation of both basic and clinically relevant questions. By standardizing methods across different PET scanners and multiple PET tracers, the Core has demonstrated the feasibility of large-scale, multi-center PET studies. Data managed and disseminated by the PET Core has been critical to defining pathophysiological models of Alzheimer's disease (AD) and helped to drive methods used in modern therapeutic trials.

KEYWORDS
ADNI, Alzheimer's disease, Alzheimer's Disease Biomarkers, imaging, PET

Highlights

- The ADNI PET Core began with FDG-PET and now includes three amyloid and three tau PET ligands.
- The PET Core has standardized acquisition and analysis of multitracer PET images.
- The ADNI PET Core helped to develop methods that have facilitated clinical trials in AD.

1 | INTRODUCTION

The PET Core of the Alzheimer's Disease Neuroimaging Initiative (ADNI) at its inception 20 years ago was markedly different from the PET Core of today. Major advances in positron emission tomography (PET) radiopharmaceuticals have driven much of this change. Indeed, throughout its life, the ADNI PET Core has been characterized by the flexible adoption of new PET tracers and helped expand our understanding of the utility of biomarkers in defining the neurobiology of Alzheimer's disease (AD). In addition, sharing data across

multiple laboratories and institutions has made possible new, harmonized approaches to the analysis of PET data to provide large, robust, longitudinal databases that are accessible to the scientific community. This article will approach the ADNI PET Core from a historical perspective, as this provides a unique view of how technical advances have helped to improve our understanding of AD and ultimately laid some of the groundwork that helped lead to a critical role for PET in the approval of new medications for its treatment.

2 | BACKGROUND: PET IMAGING BEFORE ADNI

At the start of ADNI, AD was a probabilistic diagnosis largely defined by the exclusion of alternative causes of the dementia syndrome. Since there were no specific biological or biomarker measurements during life that could confirm the diagnosis, probable and possible AD were the clinical terms that were applied, and "definite" AD was limited to confirmation by autopsy.[1] Neuroimaging occupied a relatively limited role in clinical diagnosis, with MRI used to exclude structural and non-Alzheimer causes of dementia syndrome.[2] However, both MRI and PET imaging revealed alterations in structure and function that became widely applied in research and began to influence thinking about the use of imaging biomarkers in clinical trials.

PET imaging of blood flow and glucose metabolism (the latter using [^{18}F]fluorodeoxyglucose, or FDG) showed substantial reductions in patients with AD in temporal and parietal cortex[3–5] that became widely viewed as sensitive and specific for the detection of AD in some situations. Imaging-pathology correlation studies confirmed the association between these characteristic patterns of functional change seen with FDG-PET and the presence of plaque and tangle pathology.[6–8] Most importantly, a number of studies indicated that these patterns of reduced metabolism could be detected in people at risk of AD who had not yet expressed overt symptoms; other studies also indicated that hypometabolism correlated well with symptoms. These studies either followed people longitudinally, or associated metabolic alterations with genetic risk for AD, to show that FDG could detect glucose metabolism alterations in asymptomatic or presymptomatic people.[9–11] In addition, a number of longitudinal FDG-PET studies showed that the reductions over time were sufficiently robust that they might reduce sample sizes required to detect a treatment effect and, thus, could be used as outcome measures to follow the effects of therapeutic interventions.[12,13] In fact, FDG-PET was beginning to become incorporated into clinical trials as a measure of drug efficacy.[14,15]

These studies set the stage for the inclusion of FDG-PET imaging in the initial phase of ADNI. Because ADNI was conceived as a model for clinical trials, the data suggesting that FDG-PET might increase the power to detect intervention outcomes supported its inclusion as an ADNI modality. As it evolved, it gradually became clear that while FDG-PET imaging improved our understanding of AD, it did not track the fundamental pathology of the disease, which manifested as a lack of specificity. For this reason, FDG did not become a widely used surrogate marker of drug efficacy.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed for ADNI PET Core publications. Lists were supplemented with authors' own bibliographies relating to peer-reviewed research emanating from the PET Core
2. **Interpretation**: The results of ADNI PET Core activities have contributed substantially to the current model of AD pathogenesis, and through the efforts at standardization have helped amyloid and tau PET scanning diffuse into the scientific community, laying groundwork for new approaches to clinical trials.
3. **Future directions**: ADNI investigators recognize the importance of increasing the number of different amyloid and tau ligands, as well as the diversity of the research cohort. These enhancements will make the results of ADNI more generalizable.

2.1 | ADNI-1: FDG-PET and the beginnings of amyloid PET

At the start of ADNI-1, the idea of standardizing FDG-PET across 60 imaging laboratories was daunting to the PET Core investigators. Laboratories were generally invested in using their own approaches to collecting such data, and there was no consensus about how to acquire and analyze FDG-PET multi-site images. Should the scans be acquired for 10 min, 20 min, or longer? At what time after tracer injection should the scans be acquired? What was an appropriate dose of tracer? Should we attempt to collect data describing the input function using an image-derived approach or by venous blood sampling? Even questions as simple as what the state of the participant should be during the FDG uptake phase – resting, performing a task, eyes open, eyes closed? – required months of discussions in order to reach an agreement. At the end of the process, acquisition standards centered on simplicity and were based on the realization that the expertise and interests of the ADNI sites varied considerably. The protocol simply required an injection of 5 mCi of tracer, data collection 30–60 min following injection, and participants in eyes open and ears unoccluded state.

In addition to different acquisition practices, instrumentation varied considerably across sites, resulting in a range of image resolution across the 60 participating sites. Scanners did not read out PET measurements in consistent units, resulting in differences in image intensity, and image display varied considerably. The PET Core instituted a number of innovative solutions to these problems that included requiring all sites to image a Hoffman brain phantom that was used to determine effective resolution so that scans could be smoothed to a common isotropic resolution of 8 mm full width half maximum (FWHM), which at the time was the lowest standard across all cameras in the study. This work was done at the University of Michigan as part of a scan pre-processing procedure that created a single image

from sequential 5 min frames acquired from 30 to 60 min, standardized intensity through normalization, and created images with standard orientation and voxel size.[16] This standardization of acquisition and harmonization of images from different scanners paved the way for quantitative image outcomes that could be merged or directly compared.

Two fundamental approaches to data analysis were adopted. The first was a region of interest (ROI) based approach developed in standard anatomical atlas space by selecting the coordinates of brain regions frequently cited as abnormal in FDG-PET studies of AD and mild cognitive impairment (MCI). These were identified in a literature meta-analysis and were consequently called a "meta-ROI".[17] The process produced five ROIs sampling regions in the right and left lateral temporal and parietal cortex as well as a single bilateral medial parietal cortex region that could be combined into a single meta-ROI. By spatially warping individual FDG images to standard Montreal Neurological Institute (MNI) atlas space, values for FDG-PET both cross-sectionally and longitudinally could be obtained to maximize the detection of AD-specific FDG signal. The results of this study indicated strong effect sizes for contrasts between ADNI patients and controls and strong correlations between longitudinal changes in metabolism and cognitive and functional assessments. Crucially, modeling the use of the metaROI as an outcome in a clinical trial produced sample size estimates of 180 subjects per arm compared to 312 for a cognitive measure, the Alzheimer's Disease Assessment Scale-cognitive subscale[18] (ADAScog) and 300 for a functional measure, the Functional Activities Questionnaire[19] (FAQ).[17]

A second approach to data analysis employed a whole brain voxel-wise method to define brain regions most sensitive to change over time. This had the advantage of a data-driven, unbiased approach for the estimation of longitudinal change that can be highly sensitive. However, the drawback of the approach is that it may reflect overfitting of the specific data set used to define the most sensitive voxels and it thus requires replication. ADNI investigators used separate training and test data sets to characterize 12-month metabolic declines. Using statistical parametric mapping (SPM), the optimal combination of voxels and statistical thresholds was selected in the training set and then applied to the test set.[20]

FDG data were collected in ADNI for many years, with gradual reductions in data collection until the complete cessation of FDG-PET acquisition with the start of ADNI-4. The reasons for reducing FDG-PET data collection included the increasing recognition of the non-specificity of this tracer as a biomarker for AD, an increasing emphasis on earlier stages of disease progression (before FDG changes can be detected), and concerns about exposing participants to excessive radiation as amyloid and tau PET imaging became included in the protocol. However, the overall efforts over many years have produced a large FDG-PET dataset. At this time, there are over 3500 scans available, with 858 individuals having 2 or more scans and 218 individuals with 5 or more sequential scans (spanning 4.5 ± 2.3 years of follow-up in this group) in what is likely the largest repository of FDG-PET focused on aging and dementia. These data were collected in cognitively normal people and MCI and AD patients. The scans have been used to study clinical applications, diagnosis, therapeutic outcomes, and pathophysiological mechanisms. All images are available on the LONI image repository, and numerical summary data are available as well.

The field of PET imaging in AD was revolutionized with the development of [^{11}C]PIB (Pittsburgh Compund B), the first amyloid PET radiotracer, in 2004, which made it apparent that imaging the fundamental biology and pathology of AD was possible.[21] While FDG-PET continued as an important modality, [^{11}C]PIB imaging was added to ADNI-1 as a pilot project with a limited sample size. The short half-life of the [^{11}C] label required an onsite cyclotron and radiochemistry program, limiting the number of sites that could participate and the number of individuals ultimately recruited. These early ADNI PIB-PET studies, for example, discerned relationships between amyloid and brain atrophy,[22] glucose metabolism and cognition,[23] and examined the use of amyloid PET in gene association studies.[24] Only 103 participants including controls, MCI, and AD were enrolled, with some participants undergoing serial scans, and these PIB-PET data helped to form the basis for a reconceptualization of AD pathophysiology. Together with the multisite harmonized acquisition and pre-processing approaches that had been developed and validated with ADNI FDG-PET scans, these studies paved the way for widespread amyloid PET using commercially produced ligands that became important methods in subsequent phases of ADNI and gradually made their way to therapeutic trials.

3 | THE PET CORE IN ADNI-GO, ADNI-2, AND ADNI-3

The growth of amyloid PET imaging occurred in tandem with the development of new ADNI protocols and had a profound impact on the field of AD research. [^{11}C]PIB was widely applied throughout the world, with many laboratories contributing publications on relationships between brain β-amyloid (Aβ) deposition and other features of disease. At the same time, CSF measurement of Aβ and total and phosphorylated tau contributed to models of AD pathophysiology. As studies using PIB-PET, CSF biomarkers, MRI, and FDG-PET proliferated, investigators began to examine how biomarkers were related to one another and to clinical features of the disease. This resulted in a model of AD that reflected earlier molecular hypotheses about an "amyloid cascade",[25] which would have a profound impact on ADNI protocols and priorities.

An influential early model proposing the sequential behavior of biomarkers reflecting the evolution of AD[26] suggested that measurement of Aβ with PET or CSF, tau with CSF, and neurodegeneration either via MRI or FDG PET could be used to investigate AD pathophysiology, with results over the years largely confirming a sequence of events in which Aβ is the initial step that provokes tau spread that in turn leads to neurodegeneration and cognitive decline. While this model and its instantiation as the "Jack curves" is now widely accepted (though still debated), early data accumulated in ADNI helped drive this approach. The development of [^{18}F]-labeled amyloid imaging agents by

industry was a major propellant of biomarker research. As companies sought to establish their tracers in the clinic, the regulatory pathway evolved to require the demonstration of strong correlations between PET measures of amyloid acquired *ante mortem* and *post mortem* neuropathology in the same individuals. These correlations were defined in a series of papers that ultimately resulted in approval by the US Food and Drug Administration of several amyloid PET radiopharmaceuticals for the detection of brain Aβ.[27–29] The availability of [^{18}F] amyloid tracers made collection of amyloid PET across ADNI sites possible, overcoming the limitations of the PiB-PET imaging pilot in ADNI-1.

ADNI first incorporated [^{18}F]florbetapir (FBP, Amyvid) in ADNI-GO, adding [^{18}F]florbetaben (FBB, Neuraceq) in ADNI-3. Many of the initial studies using amyloid PET examined how amyloid was predictive of cognitive change and how amyloid was related to other aspects of AD measured with other biomarkers. For example, amyloid PET was found related to cognitive decline in cognitively normal people, while FDG-PET was most strongly related to cognitive decline in those already suffering from impairment.[30] This was ultimately interpreted as amyloid reflecting the early stages of AD, while FDG-PET reflected later neurodegeneration. Longer term follow-up in ADNI indicated that the presence of brain amyloid predicted subsequent cognitive decline over the ensuing 3 years in cognitively normal people.[31] A number of studies also examined relationships between CSF measurement of Aβ and PET measures, ultimately concluding that CSF becomes abnormal before PET.[32] ADNI data were also used to investigate approaches to staging the disease by examining cross-sectional patterns of amyloid accumulation.[33,34]

PET studies of brain Aβ deposition were soon complemented by the examination of alterations in tau, initially relying on CSF measures. The introduction of the [^{18}F]-labeled tau PET ligand flortaucipir (FTP, Tauvid)[35] was important for the localization of tau deposition in the brain. Initial studies performed in a number of labs indicated the potential utility of tau PET[36,37] helping to spur its eventual adoption in ADNI. FTP was also studied in an imaging-pathology correlation project, resulting in US Food and Drug Administration (FDA) approval.[38] Including tau PET starting towards the end of ADNI-2 meant that individuals being characterized for AD biomarkers now routinely had measurement of both amyloid and tau. Neurodegeneration, which could be measured using the imaging modalities of MRI or FDG-PET, added a third component to a multimodal biomarker examination. This was codified as the "ATN" staging, in which each individual could be characterized as normal or abnormal on amyloid (A), tau (T), and neurodegeneration (N).[39] Although PET played a major role, CSF or plasma measures can also be used for this staging approach.

Throughout the phases of ADNI-GO, ADNI-2, and ADNI-3 extending from 2009 to 2022, there was a substantial increase in PET scans that resulted in a large longitudinal database of amyloid and tau PET scans. During this time, it was increasingly recognized that there was a common pattern of cortical tracer uptake across multiple different amyloid imaging agents, although systematic differences in quantitation of signal across tracers complicated the process of merging data acquired with these different tracers. The Centiloid scale was developed to standardize image quantitation across multiple amyloid PET tracers by linearly fitting numerical data from paired PET scans in individuals who received an [^{18}F] tracer and PIB, which served as the gold standard due to high binding in cortex relative to other brain regions, increasing signal-to-noise. In fact, ADNI data showing linear associations between [^{18}F] tracer uptake and [^{11}C]PIB helped spur the development of this approach.[40] Data sets used for standardization were collected by scanning groups of individuals with each [^{18}F] tracer and PIB-PET[41] in order to linearly scale uptake of the [^{18}F] tracer by the amount of PiB-PET uptake. This scale is anchored at values of 0, reflecting amyloid negativity seen in cognitively normal young people and 100, reflecting mean uptake in mild-moderate dementia due to AD. The Centiloid approach allows combining amyloid PET tracers within a single study, and has become the standard approach for reporting amyloid PET results, including in trials of amyloid-lowering immunotherapies.[42] In ADNI, all amyloid PET images are currently available as Centiloids for FBB and FBP and this approach will be continued in the future.

The continued work of the ADNI sites in recruiting, follow-up and retention has produced an extensive archive of PET images. Currently (April 2024) there are 640 FBB-PET scans, 3228 FBP-PET scans, and 1685 FTP-PET scans in the data archive along with numerical summary values by ROI. In progressive stages of ADNI, new tracers were added to the study resulting in a large database of many PET images, often with multiple tracers (amyloid PET, tau PET, FDG PET) collected in the same individuals over time. The sequence of these tracer additions is shown in Figure 1. In addition to the specific scans obtained, the schedule of scanning varied over the years and differed between the standard diagnostic groups of cognitively normal, MCI, and AD. In ADNI-1, half the participants were allocated to FDG-PET scans, which were acquired on a schedule of baseline, 6 months, 12 months, 24 months, and 36 months (controls) with the addition of an 18-month scan for MCI patients and omission of the 36-month scan for AD patients. In ADNI-2, control and MCI participants underwent annual FDG and FBP scans while AD patients had scans at baseline and 24 months. In ADNI-3, a more complex schedule was instituted in which all MCI and control participants had a tau PET at the start and end of ADNI-3, but 80% of amyloid positive and 20% of amyloid negative participants had two additional tau PET scans between baseline and final scans. Patients with AD had tau PET every 2 years, and all participants had amyloid PET performed every 2 years. At the present time, the ADNI database contains substantial participant numbers with multiple tracers: 571 with amyloid, tau and FDG, 350 with amyloid and tau, 798 with amyloid and FDG, 324 with FDG only, 12 with tau and FDG, 8 with tau only, and 34 with amyloid only.

Throughout ADNI, the core labs at the University of Michigan and the University of California, Berkeley, have been responsible for preprocessing and quantitative analysis, respectively, of PET images. At Michigan, initial procedures developed for FDG-PET have been slightly modified but remain similar. Quality control (QC) includes a statistical noise check, motion assessment across temporal frames, checking for full coverage of the brain (much more problematic in older scanners), visual checks for common PET artifacts (such as normalization issues or motion between attenuation and emission scans), as well as visual and image header checks to ensure that the ADNI protocol has been

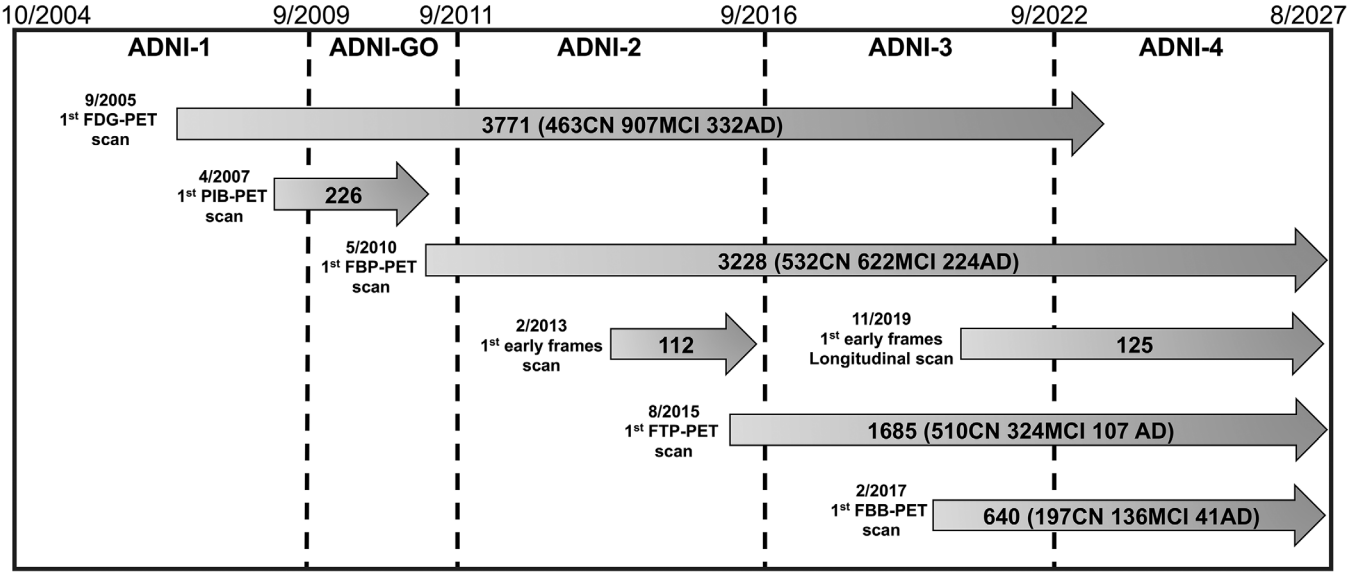

FIGURE 1 Schematic describing the PET data collected during each ADNI stage. Numbers in arrows indicate current available scan numbers for each modality as of April 2024, numbers in parentheses indicate the number of participants by diagnosis. The PIB PET sample was comprised of 19 cognitively normal, 65 MCI, and 19 AD patients. AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; MCI, mild cognitive impairment; PIB, Pittsburgh Coumpound B

followed. Data collected as sequential temporal frames are coregistered and averaged. Because all images are collected with a contemporary MRI, the MRI image for each subject is re-oriented to a common standard spatial orientation and interpolated onto a uniform image grid of 1.5 mm^3 voxels. All scans over time are registered and intensity normalized, so that all PET images for a subject can be preprocessed with a single set of regions of interest. The Hoffman phantom data is used in the final step to smooth images with a scanner-specific 3D-Gaussian filter. Until the start of ADNI-4 the common resolution was 8 mm, with the advent of ADNI-4 it moved to 6 mm. Each individuals' scan is available in five formats in the image repository with subsequent formats derived from previous ones: (1) original data, (2) coregistered dynamic scans, (3) averaged scans, (4) intensity scaled images with a standard voxel size and orientation, and (5) stage 4 images smoothed to a common resolution.

In Berkeley, images created in the final step, which are smoothed to a common resolution, are analyzed using a standard approach that coregisters the PET to a contemporary MRI that has been segmented and parcellated with FreeSurfer (currently version 7.1). This produces a table of regional values for brain amyloid and tau that permits investigators to perform whatever reference region normalization that they choose since potential reference regions are included in the table. For amyloid scans, a prescribed target ROI is used to define the Centiloid, so that associated tabular data includes a summary standard uptake value ratio (SUVR), Centiloid value, and rating as positive or negative based on the quantitative thresholds. Tau PET data are processed similarly although a standard "Centiloid-like" scale has not been adopted and through ADNI-3 the only tau PET imaging agent used in the study has been FTP. These tau PET data are also available as partial volume corrected data using a geometric transfer matrix approach.[43] All numerical data can be downloaded from the ADNI website, which contains methods documents explaining how the data are created.

Another innovation in ADNI was the "early frames" study. It has long been known that PET data obtained immediately following tracer injection reflects cerebral perfusion using tracers that are highly extracted on the first pass. These images have potential applications as perfusion images that are hypothesized to correlate with FDG-PET and, therefore, reflect neurodegeneration. In addition, these early frame data enable examination of the effects of changes in perfusion over time (measured as R1 in dynamic models) on the tissue binding as reflected in SUVR values.[44] Two phases of early frames data acquisition occurred in ADNI, one in ADNI-2 using FBP PET and one in ADNI-3 using FBP and FBB PET and with longitudinal measurement; longitudinal studies are continuing into ADNI-4. Results from studies utilizing these scans indicate a high correlation with FDG-PET[45] and demonstrate the estimation of longitudinal perfusion changes using early frames data.[44]

The work performed during the time period spanning ADNI-GO through ADNI-3 was influential in two major ways. First, ADNI required technical approaches that could maximize signal-to-noise and standardize processing and analysis approaches in ways that could be widely translated and applied to large data sets. Many other large, multi-site studies have now been started around the United States using ADNI methods; some of these are reviewed separately in this issue. Second, the wealth of data available in ADNI allowed many early investigations of biomarker models and biomarker alterations in both clinical and preclinical AD. These papers contributed to both models and empirical approaches for developing and testing novel therapies. Below, we list some of the major publications that resulted from this work:

- Studies investigating best practices for analysis of longitudinal amyloid PET data demonstrated that a composite reference region containing white matter, or a reference region of white matter alone, provided the most robust measurements of longitudinal change.[46,47]
- FDG-PET identification of AD subtypes.[48]
- Methods for the ascertainment of an amyloid positivity threshold for FBB and conversion to centiloids.[49]
- Comparisons between amyloid imaging agents that helped lay the groundwork for the centiloid approach.[40,50]
- Early proposal of a sequential model in which Aβ drives hippocampal atrophy in turn leading to memory loss.[51]
- Demonstration of weak relationships between biomarkers of Aβ and cognition, but stronger relationships between FDG and cognition.[52]
- Comparisons between amyloid PET and CSF Aβ.[32,53]
- Identification of the earliest locations of amyloid deposition.[33,54,55]
- Demonstration that elevated amyloid levels within the normal range are predictive of decline.[56]
- Demonstration of early amyloid as a driver of tau deposition.[57]
- Analysis of the time course of amyloid deposition and rates of conversion from negative to positive scans.[58]
- Support for a unidirectional pathway from amyloid to tau to neurodegeneration.[59]
- Characterization of patients who are on the AD pathway but have tau in the normal range.[60]

In addition to these studies, ADNI PET data have been incorporated into numerous multi-center studies that have investigated the predictors of cognitive decline, modeled therapeutic trials, tested models of disease pathogenesis, and examined the utility of novel fluid biomarkers.

4 | ADNI-4 AND NEW PROCEDURES

The current phase of the ADNI PET core is again marked by several novel approaches. Most importantly the range of PET tracers has been increased with the inclusion of the most commonly used tracers for Aβ and tau. The use of [^{18}F]FBP and [^{18}F]FBB for amyloid imaging will continue, and we will add [^{18}F]NAV4694 or flutefuranol. For tau-PET, we will continue [^{18}F]FTP and will add [^{18}F]MK6240 and [^{18}F]PI2620. Amyloid imaging will be harmonized through the reporting of the Centiloid scale. Tau harmonization is a work in progress that is being conducted by multiple laboratories using numerous approaches; the increasing availability of data sets with head-to-head comparisons of tracers within the same participants will help the development of these methods. The use of a uniform region-of-interest as proposed with the CenTauR approach can provide a standard reporting method.[61] All participants in ADNI-4 who are continuing from ADNI-3 will remain on the tracers already assigned, but new participants will be assigned to amyloid and tau tracers based on proximity to radiopharmacies that can deliver the tracer while simultaneously producing sample sizes for each tracer adequate for analysis. The imaging schedule for ADNI-4 will entail an amyloid and tau PET scan for all participants every 2 years. An important goal of ADNI-4 includes comparing and validating cross-sectional and longitudinal plasma biomarker measurements through comparison to PET, particularly for measures of Aβ and tau.

Approaches to data analysis will continue to use native-space coregistered structural MRI scans, segmenting and parcellating the brain with FreeSurfer in order to maintain consistency with existing data. We currently use the most recent version of FreeSurfer (7.1), and all ADNI data are analyzed with this version. There is also an MRI-free processing pipeline that is available for rapid turnaround of quantitation (such as the clinical need for quantitation) that is highly correlated with the current method.[62] ADNI-4 has also continued to incorporate new scanner technology as adopted by sites. This includes solid-state electronics and PET-MR systems. These alterations may have benefits to image resolution over the coming years which will be evaluated as the number of new scanners increases. Furthermore, substantial sensitivity increases could lead to lower injected doses of radiopharmaceuticals.

The clinical context of PET imaging has changed considerably since the initiation of ADNI, particularly for amyloid imaging. Amyloid PET results have increasingly important clinical implications, especially in view of the clinical use of amyloid PET in establishing eligibility for amyloid lowering immunotherapy. This has motivated the development of a process to return amyloid PET results to ADNI-4 participants. Disclosing results to participants may also be important in recruiting and retaining individuals from groups that have been underrepresented in research.[63,64] In ADNI-4, all participants, regardless of diagnostic category, are asked whether they wish to receive amyloid PET results, and a detailed protocol for assessing participants' reactions to this information has been developed.[65] Images undergo quantitation by the PET core to determine amyloid positivity, and have a visual read performed by trained clinicians at UCSF. The visual read is done according to the FDA approved guidelines, and if the read and quantitation disagree a consensus conference is convened to determine a final result. Participants are provided with an image of their scan alongside representative negative and positive scans using the tracer they were studied with. The availability of visual reads and the extensive data collection about responses to the results provide considerable additional data that will be important for understanding amyloid imaging in the community. Because visual interpretation of tau PET images remains a "work in progress" there are no plans to perform a similar exercise with this modality.

5 | LIMITATIONS AND CURRENT GAPS

It is increasingly acknowledged that many groups have been excluded from AD research, and so far, ADNI is no exception to this problem. The recognition of this limitation has prompted ADNI leadership to focus on the recruitment of underrepresented groups by altering practices in many different ways, from recruitment, through screening and testing. The current PET database, while large and multimodality, suffers from limited diversity of participants, particularly in terms of the racial and ethnic composition of the sample. How this affects the

scientific validity of the data is not completely clear, but hopefully, we will learn more about this in the coming years. Through the implementation of outreach and recruitment of under-represented groups, the ADNI investigators anticipate that results from the study will better generalize to people with, and at risk for, AD.

ADNI has focused on methods and approaches that are robust, ready for clinical application, and pose minimal burden. Over the years, many different modalities and approaches have been considered and rejected for inclusion. For example, it is well recognized that inflammation plays a major role in AD pathophysiology, and there have been many discussions about inclusion of a PET radiotracer that tracks neuroinflammation. The PET Core leadership has, however, concluded that existing tracers are flawed in various ways related to either the target or the characteristics of the tracer itself. Furthermore, we emphasize tracers that can be deployed on a widespread basis through radiopharmacies. Similarly, there is a real need for testing new tracers in a "head-to-head" study design. This is particularly true for tau PET tracers. However, ADNI leadership has concluded that such studies would be burdensome to participants and would increase radiation exposure. Other studies are independently testing comparisons of tau PET tracers, and this sort of data will be forthcoming for investigators to use.

6 | CONCLUSION

Over the past 20 years, the ADNI PET Core has amassed a large database of FDG, amyloid, and tau PET images with over 1 million downloads and multiple publications. The Core is on track to complete the acquisition of its 10,000th ADNI PET scan in the current calendar year. The availability of these images and analyzed data has enabled scientists around the world to test hypotheses about the pathophysiology and evolution of AD, contributing to the development of the current model of AD pathogenesis. This database and the studies emanating from it have helped to drive therapeutic trials, which have incorporated amyloid and tau PET as screening methods and outcome measurements. In its current form, the ADNI PET Core will utilize multiple amyloid and tau PET tracers, return results of amyloid scans to participants regardless of diagnostic category, and continue longitudinal data collection. These data will also be useful for the validation of plasma AD biomarker measurements and will help drive the evolution of clinical trials and hopefully clinical care for decades to come.

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CONFLICT OF INTEREST STATEMENT

Dr. Jagust receives research funding from the NIH and Genentech, has consulted for Lilly, Biogen, Clario, and Eisai and holds equity in Molecular Medicine and Optoceutics. Dr. Rabinovici receives research support from Avid Radiopharmaceuticals, Life Molecular Imaging, GE Healthcare, and Genentech. In the past 2 years, he has served as a paid consultant to Alector, Eli Lilly, Johnson & Johnson, and Merck. Dr. Landau receives research funding from the NIH, is on the DSMB and SAB for KeifeRx and the NIH IPAT study, has received speaking honoraria from Eisai and IMPACT-AD, has consulted for Banner Health and Vaccinex and has received travel funding and other research support from IMPACT-AD and the Alzheimer's Association. Dr. Villemagne has received research grants from NHMRC (GNT2001320), the Aging Mind Foundation (DAF2255207), and NIH 2P01AG025204-16) and has been a consultant or paid speaker at sponsored conference sessions for Eli Lilly, Life Molecular Imaging, ACE Barcelona, IXICO, and AC Immune. Drs. Harrison and Koeppe report no conflicts of interest. Author disclosures are available in the Supporting information.

DATA AVAILABILITY STATEMENT

All data used in this manuscript are available to the public at the ADNI data repository at the Laboratory of Neuroimaging (http://adni.loni.usc.edu).

CONSENT STATEMENT

All participants gave informed consent through their local IRBs prior to study participation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

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Note: Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.