Alzheimer's Disease



Advanced Analytics. Intelligent Insights.

Alzheimer's Disease Landscape

With less well-defined target biology, limited availability of biomarkers and higher risk of failure, drug development in Alzheimer's disease (AD) presents complex challenges. To help sponsors successfully navigate the complexities inherent in AD trials, IXICO offers advanced neuroimaging solutions that combine deep therapeutic expertise, breakthrough AI analytics and operational agility to deliver extraordinary clinical insights in AD studies.

Alzheimer's Disease Domain Expertise

As a leading provider at the forefront of advancing AD imaging biomarkers for clinical research, IXICO is actively involved in scientific collaborations and public-private consortia including:



The pioneering scientific work and close partnerships with world renowned key opinion leaders are an integral part of our proven track record in translating and operationalizing novel biomarkers into successful neuroimaging solutions for AD clinical trials.

End-to-End Services

Our comprehensive, end-to-end services to support your Alzheimer's disease trials span across:

- Individually tailored study design and consultation to deliver requisite insights
- Enriched patient selection including optimized staging and identification of participants based on 2018 NIA-AA Research Framework
- Imaging center qualification, set-up, training and management
- Centralized image reads by renowned neuroradiologists and nuclear medicine physicians
- Rigorous analysis and assessment by highly trained specialist analysts
- · Seamless project management by a dedicated central point of contact
- Full data management and quality control of image data
- Complete PET tracer supply management service



Radiology Eligibility & Safety Visual Reads

Centralized radiology reads enhance credibility and consistency of image assessments in line with FDA recommendations. IXICO's offering includes:

- A network of world renowned neuroradiologists
- Accuracy through intra- and inter-reader variability testing
- Flexible read paradigms, whether single central over-reads or double adjudicated reads
- Accelerated turnaround through direct in-built reading workflow
- Fully configurable central read forms

For inclusion/exclusion, MRI may be used to identify pathological evidence of neurodegeneration and other relevant findings that may affect cognitive impairment or impact imaging efficacy measures. For ongoing safety review, MRI can identify new findings, such as ARIA-H or ARIA-E, new microhemorrhages, superficial siderosis, Fazekas scores and other MRI abnormalities.

Volumetric MRI (vMRI)

High-resolution MRI can directly measure atrophy, a key characteristic of AD, in relevant brain regions including the entorhinal cortex, hippocampus and precuneus.

LEAP – Powerful AI Technology

IXICO uses LEAP, a proprietary AI technology, to provide fully automated segmentation for over 150 brain structures.

Features include:

- Multi-atlas propagation method, a flexible and robust segmentation approach
- Optimized and validated segmentation for AD-specific regions including whole brain, lateral ventricles and hippocampus
- Longitudinal algorithms (LLEAP) validated for specific regions to deliver atrophy results based on AI machine-learning across longitudinal datasets

In addition to powering our vMRI solutions, LEAP can be deployed in conjunction with other methods such as diffusion MRI, functional MRI and positron emission tomography (PET), enabling the superior accuracy, rigor and efficiency inherent in LEAP algorithms to enhance performances of the paired analyses.

Boundary Shift Integral (BSI)

IXICO BSI solution is a semi-automated method for examining regional brain volume. It uses a manual delineation of the brain region at baseline for whole brain, lateral ventricles or caudate, and finds volume change by analyzing the movement of the region boundary.

Cortical Thickness Analysis

IXICO deploys cortical thickness analysis to track cortical thinning which has been shown to be a highly sensitive measure of structural change in mild cognitive impairment (MCI) and AD populations.

White Matter Hyperintensity

IXICO solution identifies and quantifies the size and location of white matter hyperintense lesions which can also be used in conjunction with our LEAP segmentation to provide local lesion load.



Advanced MRI techniques are increasingly leveraged to better understand the mechanisms that underlie AD. IXICO advanced MRI solutions include:

Diffusion MRI (dMRI)

Widespread disruptions and decline in white matter integrity have been described in patients with AD and those with MCI. Diffusion MRI techniques can assess the microstructural features of white matter and can complement volumetric imaging through:

- Corroborating findings in cortical/subcortical gray matter, revealing microstructural alternations accompanying macroscopic volume loss
- Providing a more sensitive marker than via T1 in gray matter
- Delivering novel results in white matter

IXICO provides a comprehensive suite of dMRI solutions including:

- ROI (LEAP ROI, JHU White Matter Labels)
 - Single Shell: Diffusion tensor (DTI) metrics axial, radial & mean diffusivity, fractional anisotropy
 - Multi-shell dMRI: NODDI model metrics orientation dispersion, intra & extracellular volume fractions
- Whole-brain tractography (tensor-based)
 - Structural connectivity: Connectivity matrices describing the strength of the physical connection between disparate cortical gray matter structures
 - Graph theory metrics: Graph theory-based network statistics including global efficiency, local efficiency, node degree, clustering coefficient and betweenness-centrality

Free Water Analysis

IXICO's free water analysis pipeline separates intra and extracellular diffusion effects within voxels, enhancing diffusion MRI analysis in two ways:

- The relative volume of free water in an imaging voxel (the free water index) has been posited as a sensitive measure of neuroinflammation, a key characteristic of AD.
- The free water technique can act as a corrective factor for a typical tensor-based analysis, creating endpoints that are specific to brain tissue, and not a combination of brain tissue and cerebrospinal fluid (CSF) as is typically the case.

IXICO free water pipeline is adaptive depending upon the diffusion sequence:

- Single Shell: Pasternak (2009) approach
- Multi-shell: Hoy (2014) approach

Resting State Functional MRI (rs-fMRI)

Patterns of activity within and between the resting-state networks can act as sensitive biomarkers for AD. For example, a widely reported finding in AD is that the Default Mode Network starts to break down, demonstrating reduced functional connectivity between network nodes.

MRI captures localized changes in blood oxygenation, or brain "activity", over time. Unlike PET, which requires the injection of radioactive tracers, fMRI is non-invasive. In the resting brain, fMRI identifies distinct clusters of highly correlated brain regions, or resting-state networks, that show close correspondence to the networks used when the brain is actively involved in processing.

IXICO offers two pipelines for probing resting-state networks via fMRI:

- Seed-based pipeline: Anatomical regions are defined using a corresponding anatomical scan, then the activity within each region is systematically correlated with every other region to create a functional connectivity matrix.
- ICA-based pipeline: Network structure is inferred in a data-driven manner using the independent component analysis algorithm, instead of manually defining network nodes prior to observing the fMRI data, as is done with the seed-based pipeline.

Task-based functional MRI (tb-fMRI)

In patients with AD and those with MCI, tb-fMRI can examine functional changes and study the activation of the hippocampus and other structures relevant to AD during tasks involving working memory, attention, visuospatial, motor performance and others. We develop custom tb-fMRI pipelines to meet the individual requirements of a study to ensure optimal tb-fMRI analysis for the specific research question.

Arterial Spin Labeling (ASL)

ASL is a method for classifying the degree of neurodegeneration in individuals with prodromal AD and guantitatively measure cerebral blood flow (CBF), a correlate of brain function and metabolism. Patterns and strength of ASL hypoperfusion and FDG PET hypometabolism in AD are comparable. IXICO solutions can provide regional measures of CBF in AD relevant regions of interest (ROIs).

Magnetic Resonance Spectroscopy (MRS)

Proton magnetic resonance spectroscopy (MRS) provides non-invasive, brain tissues metabolite quantification. Reductions in N-acetylaspartate (NAA), a neuronal metabolite, have been described in AD highlighting the role of MRS as a potential biochemical imaging marker in AD. Changes in NAA/Creatine and NAA/Myo-Inositol metabolite ratios have also been reported to discriminate AD from vascular dementia (VaD) and Glutamate/Creatine ratios to differentiate dementia with lewy bodies (DLB) from AD.

We offer Single-Voxel MRS acquisition in several regions of interest including posterior cingulate and inferior precuneus. IXICO MRS analysis pipeline provides relative, with respect to Creatine, and absolute metabolite quantification.



Molecular Imaging (PET)

Positron emission tomography (PET) imaging is an important tool in AD, allowing assessment of cerebral glucose metabolism, inflammation, β -amyloid deposition in the brain and accumulation of pathological misfolded tau.

Amyloid tracers are used in PET imaging to measure β -amyloid deposition in the brain, which can be detected years before onset of clinical symptoms in AD. Tau-specific PET tracers allow imaging of tau deposition in the brain at early stages of the disease, assisting in accurate diagnosis and differentiation between the various tauopathies.

PET Tracer Supply Management Service

IXICO offers complete tracer supply management services including:

- Close partnerships with PET tracer manufacturers and distributors that include established operating procedures and governance structures to ensure smooth study start-up and conduct
- Comprehensive and up-to-date distribution network information to aid optimal site selection and onboarding
- Flexible and robust operational workflows for tracer supply oversight and query resolution
- · Manufacturer-endorsed, tracer-specific reader training and read workflows

PET Imaging Analysis Capabilities

IXICO provides an extensive range of tools to utilize PET imaging in AD clinical trials including:

- PET Visual Reads
 - · Reads by nuclear medicine physicians experienced in specific tracers such as for assessment of amyloid positivity
 - Fully visual interpretation of subject tracer uptake or deployment of VisQ methodology with the aid of SUVR quantitative regional uptake tool
- Standardized Uptake Value Ratio (SUVR)
 - Measurement of tracer uptake ratio in a region of interest to the uptake in a reference region both for static PET images acquired after tracer injection, and perfusion images acquired at the time of injection
 - MRI-based:
 - Where MRI is available, deployment of subject-specific brain segmentations using LEAP to produce regional measures for all PET measures, allowing anatomically accurate results compared to using generic single subject atlases
 - Calculation of SUVR in PET native space for any region/reference region with same subject-specific segmentation
 used in MRI and PET quantitative analysis
 - PET-only analysis: Where MRI is not available, deployment of PET-specific algorithm to generate SUVRs
- PET Centiloid Scale
 - Translation of SUVR in different tracers onto a standardized scale to enable comparable results when multiple amyloid radiotracers are used within a study
- Tracer Kinetics (Dynamic PET Binding Potential)
 - Application of specific dynamic scan protocols and acquisitions to measure distribution of regional tracer uptake over time, providing information on binding potential and tracer kinetics



Advancing medicine and human health by transforming data into clinically meaningful insights.



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