CertuitAD®

Test Fact Sheet

Clinical Significance (Use)

CertuitAD is an *in vitro* immunoassay that measures plasma tau protein fragments phosphorylated at threonine 217 (P-tau217), using the Quanterix SP-X Imaging and Analysis System™. CertuitAD is intended to be used in patients aged 60 years and older who present with cognitive impairment and who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline.

The CertuitAD test should be used as part of a comprehensive diagnostic work-up. It is reported as a qualitative result (*positive, negative,* or *indeterminate*). Assay results correlate highly with the presence or absence of amyloid deposition as measured by amyloid PET scan. In a clinical validation set, a positive result had a sensitivity of 91%, a negative result had a specificity of 90%, and 18% of results were indeterminate.*

This test by itself cannot establish a diagnosis of AD and is not a substitution for thorough clinical evaluation. As with any diagnostic test, physicians should consider the test result and assay performance characteristics in conjunction with other clinical findings such as individual cognitive assessment, other laboratory/imaging findings, and genetic testing.

This laboratory developed test (LDT) is not intended to be used as a screening or stand-alone diagnostic test and is not intended for therapeutic monitoring.

*Reported values for sensitivity (of a positive result) and specificity (of a negative result) were calculated without including indeterminate results. Similarly, an indeterminate result does not have a calculated sensitivity or specificity.

Clinical Background/Disease Overview

Historically, AD has been defined as a clinical syndrome of cognitive impairment with two hallmark neuropathologies in brain tissue: neuritic (amyloid) plaques and neurofibrillary tangles (NFTs) composed of tau protein. These pathologies underlay neuropathological definitive diagnosis for decades and formed the basis for diagnostic criteria originally published by the National Institute on Aging and the Alzheimer's Association (NIA-AA).[1,2] Outside of tissue assessment, in-life diagnosis of Alzheimer's disease was traditionally largely based on symptomatic presentation and elimination of alternate etiologies for cognitive and neurobehavioral changes. The emergence of PET tracers and CSF assays with high sensitivity and specificity for detection of amyloid and tau pathology has facilitated an evolution towards a *biological* definition of AD. The biological construct for AD was originally built on assessment of three principal pathologies: amyloid plaques, NFTs composed of tau protein, and neurodegeneration, i.e., the "ATN" model initially proposed as a research framework by NIA-AA.[3,4] The ATN construct allowed for a biomarker-based categorization of a disease spectrum, the Alzheimer's continuum which included both amyloid-related pathologic changes and AD itself; the former was defined by evidence of amyloid pathology only, while AD was defined by evidence of both amyloid and tau pathologies, with or without neurodegeneration.[2]

In 2024, the AA outlined a more comprehensive biomarker construct which incorporated and expanded beyond the original ATN framework. The revised AA biomarker categories include a Core Biomarker category that is essential for diagnosing AD pathology. In particular, Core 1 Biomarkers correspond to amyloid pathology as detected by amyloid PET, and these analytes in CSF or plasma include amyloid beta peptides and phosphorylated forms of tau (P-tau), modified specifically at positions 181, 217, and 231.[5]

Until recently, laboratory assessment for amyloid beta peptides or P-tau forms was limited to CSF analysis, and development of blood-based markers has been of high importance.[6] The high diagnostic accuracy of plasma P-tau, as compared to CSF testing and/or amyloid PET, has been demonstrated in multiple studies, and assays measuring P-tau217 in particular, show higher accuracy for detection of amyloid pathology versus P-tau181 and other plasma biomarkers.[7,8,9,10] Plasma P-tau217 also has higher diagnostic specificity than P-tau181 in discriminating AD from other neurodegenerative diseases.[8] Given the potential applicability of this testing in routine practice, guidelines for assay performance and the clinical use of blood-based biomarker testing during evaluation of patients with suspected AD have been published.[11,12,13]

CertuitAD specifically measures fragments of tau phosphorylated at position 217, and has shown a strong correlation with amyloid PET scan in a cohort of 2071 clinical trial participants, using a PET positivity cut-off of 24 Centiloids, i.e., early phase disease. Thus, CertuitAD may aid in the early evaluation of AD in patients experiencing cognitive decline.

Individuals Suitable for Testing

Patients aged 60 years and older who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline. This test must be ordered by a health care provider.

Clinical Test Method

Chemiluminescent immunoassay.

Test Limitations

CertuitAD results must be interpreted in the setting of a thorough clinical evaluation. CertuitAD is not intended to be used as a screening or stand-alone diagnostic test and is not intended for therapeutic monitoring. A positive result by itself does not establish a diagnosis of AD. Additional laboratory testing (such as *APOE* genotyping) may be warranted based on the patient's clinical presentation and/or family history.

Clinical Characteristics

Clinical validation of CertuitAD was performed in a large, multicenter trial population of 2071 participants aged 60 and over who presented with cognitive decline, consisting of 53% females and 47% males, with 89% participants self-identifying race as White, 6% as Asian, 5% as Black, and <1% as other racial groups, and with 16% identifying as Hispanic/Latino by ethnicity.

In this trial population, a positive CertuitAD result demonstrated a positive predictive value (PPV**) of 95%, as compared to amyloid PET scan result. PPV represents the probability that a patient will have a disease or condition (in this case, amyloid deposition), given a positive test result.

In the same trial population, a negative CertuitAD result demonstrated a negative predictive value (NPV**) of 84%, as compared to amyloid PET scan result. NPV represents the probability that a person does not have a disease or condition (in this case, amyloid deposition), given a negative test result. It is worthwhile to note that in trial participants carrying the *APOE* ε*4* genotype (hetero- or homozygous), the NPV of a negative CertuitAD result decreased to 65%. Therefore, correlation of a negative result with genetic testing may be warranted if there is strong clinical suspicion for Alzheimer's disease, bearing in mind that the clinical risk conferred by *APOE* status varies with race and ethnicity.[14]

**Indeterminate results were not included in PPV and NPV calculations.

Interpretive Information

A test result reported as **negative** is consistent with absence of amyloid deposition in brain as measured by amyloid PET scan, using a cut-off <24 Centiloids to define a negative scan. A negative CertuitAD result reduces the likelihood that a patient's cognitive impairment is due to AD.

A test result reported as **positive** is consistent with the presence of amyloid deposition in brain as measured by amyloid PET scan, using a cut-off of ≥24 Centiloids to define a positive scan. Note that a positive CertuitAD result by itself does not establish a diagnosis of AD or other cognitive disorder.

A test result reported as **indeterminate** indicates that amyloid plaques may or may not be present. Additional diagnostic testing, such as other laboratory testing or amyloid PET scan, should be considered based on clinical presentation. If symptomatology persists or evolves, repeat testing may be helpful.

CertuitAD results must be interpreted in conjunction with other patient clinical information, which may include other laboratory and radiographic findings, as well as genetic testing. CertuitAD is not intended to be used as a screening or stand-alone diagnostic test and is not intended for therapeutic monitoring.

LDT Statement and Geographic Limitations

This laboratory developed test (LDT) was developed and its performance characteristics determined by Eli Lilly Clinical Diagnostics Laboratory, LLC (ELCDL). The U.S. Food and Drug Administration (FDA) has not approved or cleared this test. ELCDL is a CAP (College of American Pathologists) accredited laboratory and is certified under CLIA (Clinical Laboratory Improvement Amendments) as qualified to perform high complexity clinical testing.

This is an LDT for use in the United States and may not be available in all states due to state licensure requirements.

References/Supporting Literature

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