

Overview

Useful For

Assessment of adults with cognitive impairment being evaluated for Alzheimer disease (AD) and other causes of cognitive impairment.

Highlights

Measurement of beta-amyloid (1-42)(A β 42), total-Tau, and phosphorylated-Tau (p-Tau) in cerebrospinal fluid (CSF) is useful in the differential diagnosis of Alzheimer Disease (AD) and other causes of cognitive impairment.

These assays are being proposed as an alternative/adjunct to imaging studies to assess AD pathology.

The p-Tau/A β 42 ratio provides excellent concordance with amyloid positron emission tomography (PET) scan to assess the presence of amyloid deposition in patients with AD.

Method Name

Electrochemiluminescent Immunoassay

NY State Available

Yes

Specimen

Specimen Type

CSF

Specimen Required

[Patient Preparation: For 12 hours before specimen collection do not take multivitamins or dietary supplements containing biotin \(vitamin B7\), which is commonly found in hair, skin, and nail supplements and multivitamins.](#)

Supplies: Alzheimer's Disease Evaluation (ADEVL) Collection Kit (T836)

Collection Container/Tube: CSF AD Biomarker Tube; specimens not collected in this tube will be rejected

Specimen Volume: 2 mL

Collection Instructions:

1. Perform lumbar puncture and discard the first 1 to 2 mL of cerebrospinal fluid (CSF).
2. Collect 2 mL of CSF directly into CSF AD Biomarker Tube. Do not aliquot. Analysis needs to be performed using collection tube.

Forms

If not ordering electronically, complete, print, and send a [Neurology Specialty Testing Client Test Request](#) (T732) with the specimen.

Specimen Minimum Volume

See Specimen Required

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	Reject
Any tube other than CSF AD Biomarker Tube	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
CSF	Frozen (preferred)	30 days	BlueTop SARSTEDT
	Refrigerated	14 days	BlueTop SARSTEDT
	Ambient	12 hours	BlueTop SARSTEDT

Clinical and Interpretive
Clinical Information

Currently the diagnosis of probable Alzheimer disease (AD) is made based on clinical symptoms, largely by the exclusion of other causes of dementia, with postmortem evidence of AD pathology required to confirm the diagnosis. Two common neuropathologic features found in the brains of patients with AD are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (tubulin-associated unit) proteins. These 2 groups of molecules are the most established biomarkers of the disease used in clinical and research practice. Positron emission tomography (PET) imaging using FDA-approved amyloid radiotracer to visualize the presence of amyloid lesions in the cerebral cortex is available in some specialized centers. Measuring Abeta peptides and Tau proteins in cerebrospinal fluid (CSF) is being proposed as an alternative/adjunct to imaging studies to assess AD pathology. Recently the use of these biomarkers has been included in the new consensus research diagnostic criteria for AD, mild cognitive impairment (MCI), and preclinical AD, proposed by the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework.

The CSF assays included in this evaluation are beta-amyloid (1-42; Abeta42), total-Tau (t-Tau) and phosphorylated-Tau (p-Tau).

Abeta42 is approximately 4 kDa protein of 42 amino acids that is formed following proteolytic cleavage of a transmembrane protein known as amyloid precursor protein (APP). Due to its hydrophobic nature, Abeta42 has the propensity to form aggregates and oligomers. Oligomers form fibrils that accumulate into amyloid plaques. These pathological changes in Abeta42 are reflected by the decrease in the CSF concentrations of Abeta42 and/or by the increase in the brain uptake of specific tracers during beta-amyloid PET.

Tau is present as six isoforms in human brain tissue. These isoforms are generated by alternative splicing of the pre-mRNA. The t-Tau assay measures all these isoforms. The most common post-translational modification of Tau proteins is phosphorylation. During neurodegeneration, abnormal phosphorylation leads to the formation of intracellular neurofibrillary tangles composed of the Tau protein that has undergone hyper-phosphorylation and developed aggregates of hyper-phosphorylated Tau proteins called p-Tau. The p-Tau assay detects phosphorylated Tau at threonine 181 (p-Tau 181).

Pathological changes associated with AD are reflected by an increase in the CSF concentrations of t-Tau and p-Tau.

Increases in CSF t-Tau reflect the intensity of the neuronal and axonal damage and degeneration and is associated with a faster progression from MCI to AD. Increases in CSF p-Tau concentrations are also associated with a faster progression from MCI to AD with more rapid cognitive decline in AD patients and in mild AD dementia cases.

Reference Values

Abeta42: >1026 pg/mL

Total-Tau: < or =238 pg/mL

Phospho-Tau 181: < or =21.7 pg/mL

p-Tau/Abeta42: < or =0.023

Interpretation

An beta-amyloid (1-42; Abeta42) result greater than 1026 pg/mL is consistent with a negative amyloid positron emission tomography (PET) scan. A negative amyloid PET scan indicates the presence of no or sparse neuritic plaques and is inconsistent with a neuropathological diagnosis of Alzheimer disease (AD). An Abeta42 result greater than 1026 pg/mL is associated with a reduced likelihood that a patient's cognitive impairment is due to AD. Total Tau (t-Tau) and phosphorylated Tau (p-Tau) cerebrospinal fluid (CSF) concentrations increase approximately 2 to 3-times as much in patients with mild-moderate AD as compared to age-matched controls. A t-Tau and/or p-Tau concentration of less than or equal to 238 pg/mL and less than or equal to 21.7 pg/mL, respectively, reduces the likelihood that a patient's cognitive impairment is due to AD.

The use of p-Tau/Abeta42 ratio provides better concordance with amyloid PET scan when compared to Abeta42, p-Tau and t-Tau individually. A cut-off of 0.023 provides optimal balance between NPA (negative % agreement) and PPA (positive % agreement) when compared to amyloid PET results. A p-Tau/Abeta42 ratio of less than or equal to 0.023 has a 92% NPA with normal amyloid PET. A ratio of greater than 0.023 has a 92% PPA with abnormal amyloid PET.

High CSF t-Tau protein concentrations are found in other neurodegenerative diseases such as prion disease or Creutzfeldt-Jakob disease (CJD). In this situation, an elevated t-Tau concentration and an increased t-Tau to p-Tau ratio has a very high specificity for differential diagnoses of CJD.

Abnormal (+)/Normal (-)	Individual comments for AD reporting values
Abeta42 (-) Phospho Tau (-) Total Tau (-)	Normal concentrations of Abeta42, phospho-Tau, and total-Tau concentrations are present in CSF. These results are not consistent with the presence of pathological changes associated with Alzheimer's disease.
Abeta42 (+) phospho-Tau (-) total-Tau (-)	Abnormal Abeta42 concentrations are present in CSF. Phospho-Tau and total-Tau concentrations are normal. These results may be consistent with Alzheimer's related pathologic change.

<p>Abeta42 (+) phospho-Tau (+) total-Tau (-)</p>	<p>Abnormal Abeta42 and phospho-Tau concentrations are present in CSF.</p> <p>The total-Tau concentration is normal.</p> <p>These results are consistent with the presence of Alzheimer's disease.</p>
<p>Abeta42 (+) phospho Tau (+) total Tau (+)</p>	<p>Abnormal Abeta42, phospho-Tau and total-Tau concentrations are present in CSF. These results are consistent with the presence of Alzheimer's disease.</p>
<p>Abeta42 (+) phospho Tau (-) total Tau (+)</p>	<p>Abnormal Abeta42, and total-Tau concentrations are present in CSF.</p> <p>The phospho-Tau concentration is normal.</p> <p>These results may be consistent with Alzheimer's related pathologic change.</p>
<p>Abeta42 (-) phospho-Tau (+) total-Tau (-)</p>	<p>Abnormal phospho-Tau concentrations are present in CSF.</p> <p>Abeta42 and total-Tau concentrations are normal.</p> <p>These results are not consistent with the presence of pathological changes associated with Alzheimer's disease.</p>
<p>Abeta42 (-) phospho tau (-) total-Tau (+)</p>	<p>Abnormal total-Tau concentrations are present in CSF.</p> <p>The Abeta42 and phospho-Tau concentrations are normal.</p> <p>These results are not consistent with the presence of pathological changes associated with Alzheimer's disease.</p>

Abeta42 (-)	Abnormal phospho-Tau and total-Tau concentrations are present in CSF.
phospho-Tau (+)	
total-Tau (+)	
	The Abeta42 concentration is normal.
	These results are not consistent with the presence of pathological changes associated with Alzheimer's disease.

This table and interpretations are based on the National Institute on Aging and Alzheimer's Association research framework diagnostic recommendations. (See Jack CR Jr. et al: *Alzheimers. Dement.* 2018;14:535-562)

Cautions

A positive cerebrospinal fluid (CSF) beta-amyloid 42 (Abeta42), total Tau (t-Tau), or phosphorylated Tau (p-Tau) result, or p-Tau/Abeta42 ratio does not establish a diagnosis of Alzheimer disease (AD) or other cognitive disorder. These results should be interpreted in combination with other clinical diagnostic and radiologic evaluations.

These assays should not be used to predict the development of dementia or other neurologic conditions or to monitor response to therapies.

Failure to adhere to the sample collection instructions provided may result in falsely low Abeta42 concentrations and potential misdiagnosis of AD due to the binding of Abeta42 to the surface of the tube.

Clinical Reference

1. Lifke V, Kollmorgen G, Manuilova E, et al: Elecsys Total-Tau and Phospho-Tau (181P) CSF assays: Analytical performance of the novel, fully automated immunoassays for quantification of tau proteins in human cerebrospinal fluid. *Clin Biochem.* 2019 Oct;72:30-38
2. Willemse EAJ, van Maurik IS, Tijms BM et al: Diagnostic performance of Elecsys immunoassays for cerebrospinal fluid Alzheimer's disease biomarkers in a nonacademic, multicenter memory clinic cohort: The ABIDE project. *Alzheimers Dement (Amst).* 2018 Sep 12;10:563-572
3. Hansson O, Seibyl J, Stomrud E et al: CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement.* 2018 Nov;14(11):1470-1481
4. Schindler SE, Gray JD, Gordon BA, et al: Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimers Dement.* 2018 Nov;14(11):1460-1469

Performance

Method Description

Beta-amyloid (1-42) CSF:

The Roche cobas assay for determining beta-amyloid (1-42) in cerebrospinal fluid (CSF) uses a sandwich assay principle. A biotinylated monoclonal beta-amyloid (1-42) antibody (21F12) and a monoclonal beta-amyloid (1-42)

specific antibody (3D6) labeled with a ruthenium complex react to form a sandwich complex. Streptavidin-coated microparticles are added, and the interaction between biotin and streptavidin allows the complex to become bound to the solid phase. The reaction mixture is then aspirated into the measuring cell, microparticles are captured onto the electrode, and the application of voltage induces chemiluminescent emission, which is measured by a photomultiplier. (Package Insert: Roche Elecsys beta-amyloid (1-42) CSF, Roche Diagnostics Corp, 09/2019)

Total-Tau CSF:

The Roche cobas assay for determining total-Tau in CSF uses a sandwich assay principle. Two biotinylated monoclonal Tau-specific antibodies (5.28.464 and 4.35.411) and a monoclonal Tau-specific antibody (PC1C6) labeled with a ruthenium complex react to form a sandwich complex. Streptavidin-coated microparticles are added, and the interaction between biotin and streptavidin allows the complex to become bound to the solid phase. The reaction mixture is then aspirated into the measuring cell, microparticles are captured onto the electrode, and the application of voltage induces chemiluminescent emission, which is measured by a photomultiplier. (Package Insert: Roche Elecsys Total-Tau CSF, Roche Diagnostics Corp, 10/2019)

Phospho-Tau CSF:

The Roche cobas assay for determining phospho-Tau in CSF uses a sandwich assay principle. A biotinylated monoclonal antibody specific for phosphorylation at threonine 181 (11H5V1) and a monoclonal Tau-specific antibody (PC1C6) labeled with a ruthenium complex react to form a sandwich complex. Streptavidin-coated microparticles are added, and the interaction between biotin and streptavidin allows the complex to become bound to the solid phase. The reaction mixture is then aspirated into the measuring cell, microparticles are captured onto the electrode, and the application of voltage induces chemiluminescent emission, which is measured by a photomultiplier. (Package Insert: Roche Elecsys pTau (181P) CSF, Roche Diagnostics Corp, 08/2019)

PDF Report

No

Day(s) and Time(s) Test Performed

Tuesday, Thursday 6 p.m.

Analytic Time

1 day

Maximum Laboratory Time

8 days

Specimen Retention Time

3 months

Performing Laboratory Location

Rochester

Fees and Codes**Fees**

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

83520 x 3

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
ADEVL	Alzheimer's Disease Evaluation, CSF	In Process

Result ID	Test Result Name	Result LOINC Value
PTABR	p-Tau/Abeta42	41027-4
ADINT	AD Interpretation	69048-7
AB42P	Abeta42	33203-1
TTAUP	Total-Tau	30160-6
PTAUP	Phospho-Tau(181P)	72260-3