MAYO CLINIC LABORATORIES

# Test Definition: RPDE

Rapidly Progressive Dementia Evaluation, Spinal Fluid

## Overview

### Useful For

Evaluation of individuals presenting with rapidly progressive dementia of uncertain disease etiology and a differential diagnosis of Creutzfeldt-Jakob disease and rapidly progressive Alzheimer disease

### Profile Information

| Test Id | Reporting Name | Available Separately | Always Performed |
|---|---|---|---|
| RPDEI | RPD Eval Interp, CSF | No | Yes |
| RTQPC | RT-QuIC Prion, CSF | No | Yes |
| TTPTQ | t-Tau/p-Tau | No | Yes |
| ADRTQ | Alzheimer's Disease Evaluation, CSF | No | Yes |

### Special Instructions

• Spinal Fluid Specimen Collection Instructions for Creutzfeldt-Jakob Disease and Rapidly Progressive Dementia Evaluations

### Method Name

RPDEI: Medical Interpretation
RTQPC: Real-Time Quaking-Induced Conversion (RT-QuIC)
TTPTQ: Calculation
ADRTQ: Electrochemiluminescent Immunoassay (ECLIA)

### NY State Available

Yes

## Specimen

### Specimen Type

CSF

### Ordering Guidance

In individuals with a high clinical suspicion of Alzheimer disease, order ADEVL / Alzheimer Disease Evaluation, Spinal Fluid.

This test can only be performed on specimens collected and transported in polypropylene tubes. If this test is ordered and a polystyrene tube is received, it will be canceled and automatically reordered by the laboratory as CJDE /

Creutzfeldt-Jakob Disease Evaluation, Spinal Fluid.

For cases where there is high suspicion of human prion disease supported by clinical or paraclinical magnetic resonance imaging features, order CJDE / Creutzfeldt-Jakob Disease Evaluation, Spinal Fluid.
Early in the disease course, or in atypical cases, the disease progression may be slower and include significant clinical overlap (dementia, rigidity, myoclonus) with other potential causes of rapidly progressive dementia, including Alzheimer disease. In the latter case, it would be more appropriate to order this test.

## Specimen Required

**Supplies**: CJD/RPD Evaluation Kit (T966)
**Container/Tube:**
**Preferred:** 2 Sarstedt CSF False Bottom Tubes 63.614.625 (2.5 mL)
**Acceptable:** Sarstedt 72.703.600 (1.5 mL) or Sarstedt 72.694.600 (2 mL)
**Specimen Volume:** 2 tubes; each containing 1.5 to 2.5 mL
**Collection Instructions:**
1. Perform lumbar puncture and discard the first 1 to 2 mL of cerebrospinal fluid (CSF).
2. Collect two tubes of CSF directly into an acceptable collection tube until the tube is at least 50% full.
3. Send CSF specimen in original collection tube. **Do not aliquot.**
**Note: Polystyrene collection tubes are not acceptable.** Exposure of CSF to polystyrene tubes may result in falsely low Abeta42 concentrations.
The Alzheimer's Association consensus protocol for handling of CSF for clinical measurements of Abeta42 and tau recommends using the drip method for CSF collection and directly collecting into a low-bind polypropylene tube. Although some clinicians prefer the syringe pull method due to speed of collection, the drip method reduces the risk of Abeta42 binding to the plastic of any syringe used.
4. Collection instructions can also be found on Spinal Fluid Specimen Collection Instructions for Creutzfeldt-Jakob Disease and Rapidly Progressive Dementia Evaluations (T974).

## 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 | Reject |
| Gross icterus | Reject |
| Discolored CSF | Reject |

## Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| CSF | Frozen (preferred) | 28 days | BlueTop SARSTEDT |
| | Ambient | 12 hours | BlueTop SARSTEDT |
| | Refrigerated | 14 days | BlueTop SARSTEDT |

## Clinical & Interpretive

### Clinical Information

Primary rapid progressive dementia (RPD) occurs in human prion diseases, rapidly progressive types of other neurodegenerative dementias (Lewy Body dementia, Alzheimer disease), autoimmune central nervous system (CNS) disorders and other conditions that involved rapid neuronal damage. Based on data from tertiary medical centers, when there is high clinical suspicion of Creutzfeldt-Jakob disease (CJD), a majority will be proven to be CJD upon autopsy. However, in those where CJD has been ruled out either by additional diagnostic testing or autopsy, the most common differential diagnoses include rapidly progressive Alzheimer disease or autoimmune CNS disease. Distinguishing these diseases is often challenging, and the use of cerebrospinal fluid (CSF) biomarker testing is an important tool in establishing the correct diagnosis.

CJD is a rare and fatal neurodegenerative disorder that predominantly affects the brain and is caused by misfolded prion proteins (PrP[Sc]). CJD accounts for more than 90% of human prion diseases. Initial symptom onset is heterogenous but commonly includes rapidly progressive dementia, cerebellar ataxia, and myoclonus. The timeline of symptom progression and the pattern of symptom evolution can be divergent across patients and CJD subtypes, making an accurate diagnosis based on clinical presentation alone challenging. The inclusion of biomarkers with high diagnostic accuracy has improved the differentiation of CJD and related prion diseases from treatable neurological conditions with overlapping phenotypes. The real-time quaking-induced conversion (RT-QuIC) assay in CSF has been established to have strong clinical utility for early and accurate diagnosis of CJD through numerous independent studies. Furthermore, the robustness and reproducibility of the RT-QuIC assay for CJD across laboratories has been demonstrated through international ring trials. The clinical sensitivity and specificity of second-generation RT-QuIC assays in CSF have been consistently reported to be greater than or equal to 92% and greater than or equal to 99%, respectively. Despite the high diagnostic accuracy of the assay, RT-QuIC results should be interpreted in the appropriate clinical context along with other clinical and paraclinical findings. A definitive diagnosis of sporadic prion disease can be established only through neuropathological assessment of brain tissue.

Unexpectedly negative RT-QuIC test results should prompt careful consideration of the differential diagnosis. If there is high suspicion of prion disease, repeat RT-QuIC testing may be warranted. A small subset of cases initially negative by RT-QuIC may become positive as the disease progresses. However, RT-QuIC may be persistently negative in a small proportion of patients with definite prion disease. False-negative RT-QuIC results are most often encountered in cases of genetic prion disease (eg, fatal familial insomnia and Gerstmann-Straussler-Scheinker disease) and in atypical sporadic prion disease subtypes (eg, MM2 cortical subtype) that have slower indolent disease progression.

Other CSF biomarkers have been utilized to support the diagnosis of CJD, including 14-3-3, total Tau measurement, and the ratio of total Tau (t-Tau) to phosphorylated Tau at threonine 181. Recent studies have indicated that the Tau ratio (t-Tau to pT181-Tau or vice versa) has a very high diagnostic accuracy, which exceeds that provided by t-Tau or 14-3-3 enzyme-linked immunosorbent assays (ELISA). In a cohort of probable/definite CJD cases and controls tested utilizing the

Roche Total-Tau and p-Tau (threonine 181) Elecsys assays, the optimized cut-off value for total Tau (>393 ng/L) had a clinical sensitivity and specificity of 92.3% and 88.3% for CJD, respectively; and the optimized cut-off value for the t-Tau to p-Tau ratio (>18) has a clinical sensitivity and specificity of 97.4% and 95.9% for CJD, respectively.

Importantly, t-Tau or t-Tau to p-Tau ratios utilize assay-dependent cut-off values, and cut-off values from one assay are not transferable to different assay platforms.

Alzheimer disease (AD) is the most common cause of dementia. The pathologic changes observed in the brain of individuals with AD dementia are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (tubulin-associated unit) proteins. Accumulation of Abeta is one target for AD therapeutics. Accumulation of Abeta can be measured by amyloid positron emission tomography (PET) imaging or by measurement of Abeta42 peptides and certain phosphorylated Tau (such as p-Tau181) proteins in CSF. In particular, the use of the p-Tau181/Abeta42 ratio has been shown to be an excellent surrogate marker of amyloid plaque burden.

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. 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 amyloid-PET.

Tau is present as six isoforms in human brain tissue. These isoforms are generated by alternative splicing of the pre-messenger RNA. 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 hyperphosphorylation and developed aggregates of hyperphosphorylated Tau proteins called p-Tau. 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 concentrations reflect the intensity of the neuronal and axonal damage and degeneration and are associated with a faster progression from mild cognitive impairment (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 patients with AD and in mild AD dementia cases. The p-Tau assay used in this evaluation detects p-Tau at threonine 181.

## Reference Values

RT-QuIC PRION, CSF:
Negative

t-TAU/p-TAU:
< or =18

p-TAU/ABETA 42:
< or =0.028

BETA-AMYLOID (1-42) (Abeta42):
>834 pg/mL

TOTAL TAU:
< or =238 pg/mL (Alzheimer disease)
< or =393 pg/mL (Creutzfeldt-Jakob disease)

PHOSPHORYLATED TAU 181:
< or =21.6 pg/mL

## Interpretation

An interpretive report will be provided when no abnormal results are detected. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis and recommendations for patient management resources.

## Cautions

These test results should be interpreted in the appropriate clinical context along with other clinical and paraclinical findings. Only through neuropathological assessment of brain tissue can a definitive diagnosis of sporadic prion disease be established.

Some molecular subtypes of prion protein have been reported to have lower detectability by the real-time quaking-induced conversion (RT-QuIC) assay.

Even small quantities of blood in CSF can result in false-negative RT-QuIC results.

The presence of fluorescent substances may interfere with testing and prevent the accurate interpretation of the RT-QuIC assay.

Careful consideration of the differential diagnosis is advised when RT-QuIC test results are unexpectedly negative. Repeat testing with RT-QuIC may be warranted if there is high suspicion of prion disease. A small subset of initially negative cases by RT-QuIC may become positive as the disease progresses. However, a small proportion of patients with definitive prion disease may be persistently negative by RT-QuIC. False-negative RT-QuIC results are most often encountered in cases of genetic prion disease, such as fatal familial insomnia and Gerstmann-Straussler-Scheinker, and in atypical sporadic prion disease subtypes that have slower indolent disease progression.

Improper specimen handling or interindividual differences in overall concentration of Abeta peptide production may yield an abnormally low Abeta42 in the context of a normal p-Tau181/Abeta42 ratio. Results should be interpreted in combination with other clinical information.

Exposure of cerebrospinal fluid to polystyrene tubes can reduce concentrations of the amyloid Abeta42 by as much as 20% to 50% due to adherence of the sticky amyloid protein to polystyrene tube surface material, potentially altering clinical interpretation, including the p-Tau181/Abeta 42 ratio. P-Tau181 and total Tau protein do not substantially adhere to polystyrene collection tubes.

Failure to adhere to the specimen collection instructions provided may result in falsely low Abeta42 concentrations and potential misdiagnosis of Alzheimer disease.

In rare cases, some individuals can develop antibodies to mouse or other animal antibodies (often referred to as human anti-mouse antibodies [HAMA] or heterophile antibodies), which may cause interference in some immunoassays. The presence of antibodies to streptavidin or ruthenium can also rarely occur and may interfere in this assay. Caution should be used in interpretation of results, and the laboratory should be alerted if the result does not correlate with the clinical presentation.

### Clinical Reference

1. Hermann P, Appleby B, Brandel JP, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Lancet Neurol. 2021;20(3):235-246
2. Rhoads DD, Wrona A, Foutz A, et al. Diagnosis of prion diseases by RT-QuIC results in improved surveillance. Neurology. 2020;95(8):e1017-e1026
3. Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology. 2012;79(6):547-552
4. Shir D, Lazar EB, Graff-Radford J, et al. Analysis of clinical features, diagnostic tests, and biomarkers in patients with suspected Creutzfeldt-Jakob disease, 2014-2021. JAMA Netw Open. 2022;5(8):e2225098
5. Skillback T, Rosen C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 2014;71(4):476-483
6. Hermann P, Haller P, Goebel S, et al. Total and phosphorylated cerebrospinal fluid Tau in the differential diagnosis of sporadic Creutzfeldt-Jakob disease and rapidly progressive Alzheimer's disease. Viruses. 2022;14(2):276
7. van Harten AC, Wiste HJ, Weigand SD, et al. Detection of Alzheimer's disease amyloid beta 1-42, p-tau, and t-tau assays. Alzheimers Dement. 2022;18(4):635-644. doi:10.1002/alz.12406
8. Campbell MR, Ashrafzadeh-Kian S, Petersen RC, et al. P-tau/AB42 and AB42/40 ratios in CSF are equally predictive of amyloid PET status. Alzheimers Dement (Amst). 2021;13(1):e12190. doi:10.1002/dad2.12190
9. Blennow K, Stomrud E, Zetterberg H, et al. Second-generation Elecsys cerebrospinal fluid immunoassays aid diagnosis of early Alzheimer's disease. Clin Chem Lab Med. 2022;61(2):234-244. doi:10.1515/cclm-2022-0516
10. Jack CR Jr, Bennett DA, Blennow K, et al: NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535-562

## Performance

### Method Description

Abnormal Prion Protein:
This assay is a second-generation seeding aggregation assay known as a real-time quaking-induced conversion assay (RT-QuIC). Briefly, the cerebrospinal fluid (CSF) sample is mixed with reaction buffer that contains fluorescence emitting dye and truncated recombinant hamster prion proteins (amino acids 90-231) in a 96-well black microtiter plate with clear optical bottom. Each 96-well plate includes 2 positive controls and 2 negative controls plus 20 samples. Each sample is tested in 4 replicate wells. At completion of the reaction, if at least one of the reaction wells per sample is scored positive, testing is repeated for that sample. The assay is performed on a BMG Omega FLUOStar instrument.(Orru CD, Groveman BR, Hughson AG, et al. RT-QuIC assays for prion disease detection and diagnostics. Methods Mol Biol. 2017;1658:185-203)

Beta-Amyloid (1-42):
The Roche cobas assay for determining beta-amyloid (1-42) in CSF uses a sandwich-assay principle. A biotinylated monoclonal beta-amyloid (1-42) antibody and a monoclonal beta-amyloid (1-42) specific antibody 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: Elecsys beta-Amyloid (1-42) CSF II. Roche Diagnostics; V 1.0, 12/2022)

Total Tau:
The Roche cobas assay for determining total Tau in CSF uses a sandwich-assay principle. Two biotinylated monoclonal Tau-specific antibodies and a monoclonal Tau-specific antibody 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: Elecsys Total-Tau CSF. Roche Diagnostics; V 2.0, 10/2023)

Phospho-Tau:
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 and a monoclonal Tau-specific antibody 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: Elecsys Phospho-Tau (181P) CSF. Roche Diagnostics; V 1.0, 12/2022)

### PDF Report
No

### Day(s) Performed
Monday through Friday, Sunday

### Report Available
3 to 8 days

### Specimen Retention Time
12 months

### Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

## Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

## CPT Code Information

0584U
82234
84393
84394

## LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| RPDE | Rapid Progress Dementia Eval, CSF | 104134-2 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| PTABQ | p-Tau/Abeta42 | 41027-4 |
| ADINQ | AD Interpretation | 69048-7 |
| AB42Q | Abeta42 | 33203-1 |
| TTAUQ | Total-Tau | 30160-6 |
| PTAUQ | Phospho-Tau(181P) | 72260-3 |
| 620307 | RT-QuIC Prion, CSF | 101662-5 |
| TTPTQ | t-Tau/p-Tau | 101752-4 |
| 620377 | RPD Eval Interp, CSF | 69048-7 |