# Test Definition: CJDE

Creutzfeldt-Jakob Disease Evaluation, Spinal Fluid

## Overview

### Useful For

Assessment of Creutzfeldt-Jakob disease or other human prion disease in patients with rapidly progressive dementia

### Profile Information

| Test Id | Reporting Name | Available Separately | Always Performed |
|---|---|---|---|
| CJDEI | CJD Eval Interp, CSF | No | Yes |
| RTQPC | RT-QuIC Prion, CSF | No | Yes |
| ADCJD | Tau CJD Evaluation, CSF | No | Yes |

### Special Instructions

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

### Method Name

CJDEI: Medical Interpretation
RTQPC: Real-Time Quaking-Induced Conversion (RT-QuIC)
ADCJD: Electrochemiluminescent Immunoassay (ECLIA)

### NY State Available

Yes

## Specimen

### Specimen Type

CSF

### Ordering Guidance

In cases where there is high suspicion of human prion disease supported by clinical or paraclinical (MRI imaging) features, this test should be ordered.
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 RPDE / Rapidly Progressive Dementia Evaluation, Spinal Fluid.

### 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 mL 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.**
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
This evaluation is intended for use in patients with suspected Creutzfeldt-Jakob disease (CJD) and other human prion diseases. 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 cerebrospinal fluid (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 definitive 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 to phosphorylated Tau at threonine 181. Recent studies have indicated that the Tau ratio (total Tau to pT181-Tau or vice versa) has a very high diagnostic accuracy, which exceeds that provided by total 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 total Tau to p-Tau ratio (>18) has a clinical sensitivity and specificity of 97.4% and 95.9% for CJD, respectively.

Importantly, total Tau or total 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.

The National Prion Disease Pathology Surveillance Center (NPDPSC) coordinates autopsies and neuropathologic examinations on suspected prion disease cases. More information about services available at the NPDPSC may be found at https://case.edu/medicine/pathology/divisions/prion-center.

## Reference Values

RT-QuIC PRION, CSF:
Negative

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

TOTAL TAU:
< or =393 pg/mL

## Interpretation

A positive real-time quaking-induced conversion (RT-QuIC) is supportive of prion disease and, in the correct clinical context, fulfills the Centers of Disease Control and Prevention diagnostic criteria of probable prion disease.(1)

An elevated total Tau/p-Tau (threonine 181) ratio (>18) increases the likelihood of prion disease but can be seen in patients with rapidly progressive dementia due to other causes, including autoimmune encephalitis, central nervous system malignancy, seizure disorder, stroke, and other neurodegenerative diseases.

Negative results do not exclude the possibility of prion disease.

| | Elevated t-Tau/p-Tau ratio (>18) | Normal t-Tau/p-Tau ratio (< or =18) |
|---|---|---|
| RT-QuIC positive | Prion disease highly likely | Prion disease likely |
| RT-QuIC negative or inconclusive | Prion disease possible | Prion disease unlikely |

RT-QuIC = Real-time quaking-induced conversion

## 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 real-time quaking-induced conversion (RT-QuIC) assays.

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

The presence of fluorescent substances may interfere with testing and prevent an 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 disease, and in atypical sporadic prion disease subtypes that have slower indolent disease progression.

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. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and Pathology (DHCPP). Diagnostic criteria: CDC's diagnostic criteria for Creutzfeldt-Jakob disease (CJD), 2018. CDC; Updated October 18, 2021. Accessed July 17, 2024. Available at www.cdc.gov/creutzfeldt-jakob/hcp/clinical-overview/diagnosis.html
2. Hermann P, Appleby B, Brandel JP, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease.

Lancet Neurol. 2021;20(3):235-246
3. 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
4. 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
5. 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
6. 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
7. 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

## 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)

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)

# Test Definition: CJDE

Creutzfeldt-Jakob Disease Evaluation, Spinal Fluid

### 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
84393
84394

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| CJDE | CJD Evaluation, CSF | 97502-9 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| CTTPT | t-Tau/p-Tau | 101752-4 |
| CTTAU | Total-Tau | 30160-6 |
| CPTAU | Phospho-Tau(181P) | 72260-3 |
| 620307 | RT-QuIC Prion, CSF | 101662-5 |
| 620375 | CJD Eval Interp, CSF | 69048-7 |