



# PHLN

Public Health Laboratory Network

# Human transmissible spongiform encephalopathies (TSE)

## Laboratory case definition

The Public Health Laboratory Network (PHLN) has developed standard case definitions for the diagnosis of key diseases in Australia. This document contains the laboratory case definition for human transmissible spongiform encephalopathies.

**Authorisation:** PHLN

**Consensus date:** 2 November 2020

---

## 1 PHLN Summary Laboratory Definition

### 1.1 Condition:

Human Transmissible Spongiform Encephalopathies (TSE), including Creutzfeldt-Jakob Disease (CJD)

#### 1.1.1 Definitive Criteria

- Neuropathological confirmation of TSE supplemented by immunochemical detection of abnormal (typically protease resistant) prion protein (PrP<sup>sc</sup>) by blot OR immunohistochemistry.

**Note:** Genetic forms of TSE: Definitive criteria with a recognized pathogenic prion protein gene (*PRNP*) mutation.

#### 1.1.2 Suggestive Criteria

- Presence of 14-3-3 protein in cerebrospinal fluid (CSF).
- Real Time-Quaking Induced Conversion (RT-QuIC) of PrP<sup>C</sup> in CSF and other tissues
- PrP<sup>sc</sup> positive tonsil or other lymphoreticular tissue biopsy (variant CJD only).

**Note:** Laboratory suggestive evidence requires clinical and/or radiological and/or electroencephalogram (EEG) evidence to meet the case definition of CJD/vCJD.

### 1.1.3 Special Considerations / Guide for Use

Pre-mortem brain biopsy is not recommended as a routine procedure to confirm the clinical suspicion of TSE.

### 1.1.4 Links to related documents

- [CDNA \(clinical\) case definition for Creutzfeldt-Jakob Disease](http://www.health.gov.au/casedefinitions): through (www.health.gov.au/casedefinitions) or directly at (www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd\_cjd.htm)
- [CDNA \(clinical\) case definition for Variant Creutzfeldt-Jakob Disease](http://www.health.gov.au/casedefinitions): through (www.health.gov.au/casedefinitions) or directly at (www.health.gov.au/internet/main/publishing.nsf/Content/cda-nndss-casedef-vcjd.htm)
- [CDNA The Creutzfeldt-Jakob Disease Infection Control Guidelines 2013](http://www.health.gov.au/internet/main/publishing.nsf/Content/icg-guidelines-index.htm) at (www.health.gov.au/internet/main/publishing.nsf/Content/icg-guidelines-index.htm)
- [Australian Government. Department of Health. The use of human pituitary hormones in Australia and Creutzfeldt-Jakob disease](http://www.health.gov.au/internet/main/publishing.nsf/Content/health-publth-strateg-phi-index.htm) at (www.health.gov.au/internet/main/publishing.nsf/Content/health-publth-strateg-phi-index.htm)
- [Australian Government. Department of Health. Bovine Spongiform Encephalopathy \(BSE\) in animals](http://www.health.gov.au/internet/main/publishing.nsf/Content/health-publth-strateg-bse-index.htm) at (www.health.gov.au/internet/main/publishing.nsf/Content/health-publth-strateg-bse-index.htm)

## 2 Background

### 2.1 Introduction

Transmissible spongiform encephalopathies (TSE), or prion diseases, are a group of invariably fatal neurodegenerative disorders, which may involve prolonged incubation periods (order of years to decades) after horizontal transmission in humans and animals<sup>1</sup>.

The precise biophysical nature of the agent responsible for transmission in TSEs is not fully understood, however the transmissible agent is comprised primarily, if not exclusively, by PrP<sup>sc</sup>, a misfolded conformer of the normal cellular prion protein (PrP<sup>c</sup>). The term prion is derived from the phrase “proteinaceous infectious particle”<sup>1</sup>. Both PrP<sup>sc</sup> and PrP<sup>c</sup> are encoded from the same sequence of the prion protein gene (*PRNP*); hence, the PrP<sup>sc</sup> isoform differs from the normal PrP<sup>c</sup> isoform in secondary and tertiary structure but not in primary amino acids sequence<sup>2</sup>. The PrP<sup>sc</sup> isoform is typically highly resistant to proteolysis and degradation by conventional means of chemical and physical decontamination or disinfection. In contrast, the PrP<sup>c</sup> is soluble in non-denaturing detergents and is completely degraded by proteases<sup>2</sup>. PrP<sup>sc</sup> is transmissible in the laboratory to many species, including wild-type and transgenic mice and non-human primates<sup>3</sup>. Prion diseases of humans are not transmitted through casual or intimate person-to-person contact.

There are 9 human TSE sub-types: (1) sporadic Creutzfeldt-Jakob disease (sCJD), (2) genetic CJD (gCJD), (3) iatrogenic CJD (iCJD), (4) variant CJD (vCJD), (5) Kuru, (6) Gerstmann-Sträussler-

Scheinker syndrome (GSS), (7) familial fatal insomnia (FFI), (8) sporadic fatal insomnia (sFI) and (9) variably protease sensitive prionopathy (VPSPr)<sup>2</sup>.

## 2.2 Epidemiology

sCJD accounts for most TSE cases in humans. sCJD is thought to be due to spontaneous misfolding of PrP<sup>c</sup> to form PrP<sup>sc</sup>. It is believed to occur worldwide, with an annual incidence of 1-2 cases per million population, representing approximately 85% of all CJD cases<sup>1,4</sup>. *PRNP* polymorphisms in regulatory, as well as coding sequences, have been associated with predisposition to the disease development. Homozygosity at M129V polymorphism is a risk factor for the development of sCJD. gCJD is an autosomal dominant condition with variable penetrance due to one of several sequence variations in the *PRNP*, and accounts for approximately 10-14% of cases of CJD. iCJD has been reported as a result of medical treatments including human pituitary derived growth hormone injections, dura mater and corneal tissue transplants, and brain surgery involving contaminated instruments. vCJD was first reported in the United Kingdom in 1996 and is linked to bovine spongiform encephalopathy (BSE). The most plausible route of exposure is via BSE contaminated food. Probable secondary transmission of vCJD via blood transfusion has been reported. Examination of appendix specimens in the UK has estimated the prevalence of vCJD infection as 493 per million population<sup>5</sup>. However, uncertainties exist around the susceptibility of these carriers to develop vCJD, as well as the duration of the incubation period, making predictions of future numbers of vCJD cases complicated<sup>1</sup>. vCJD has not yet been reported in Australia.

FFI is an autosomal dominant inherited human prion disease caused by the *PRNP* mutation D178N linked to the methionine of the *PRNP* polymorphism M129V. When linked to valine at the codon M129V, the same mutation usually causes gCJD<sup>2</sup>. Approximately 100 cases of FFI have been reported among 40 families. sFI presents clinically similar to FFI but without a family history and/or *PRNP* mutation, with 24 cases reported globally. GSS also has autosomal dominant inheritance, and results from several *PRNP* sequence variants. The incidence is estimated at 1 in 100 million population per year. Kuru resulted from ritualistic endocannibalism in the Fore linguistic group of Papua New Guinea Eastern Highlands. Although the incubation period may be more than fifty years, the incidence of Kuru has steadily declined since a ban on cannibalism was placed in the mid-1950s and is now considered essentially eradicated. VPSPr is the latest human prion disease to be described, and is characterised by reduced resistance of the PrP<sup>sc</sup> isoforms to proteolysis. Over 30 cases have been reported<sup>2</sup>.

## 2.3 Clinical Features

As the abnormal PrP<sup>sc</sup> accumulates in the brain, it causes massive destruction through unresolved mechanisms, which in CJD typically results in vacuolation (spongiform appearance) of the neuropil at the microscopic level. The usual age of onset of sCJD is 65-75 years. Typical CJD symptoms include rapidly progressive dementia, cerebellar dysfunction with gait and limb ataxia, pyramidal/extrapyramidal symptoms, myoclonus and eventually akinetic mutism. Approximately 60-80% of cases of sCJD are reported to develop the characteristic EEG appearance of 0.5-2Hz generalised bi/triphasic periodic complexes, with the remaining cases usually showing only non-specific slow wave abnormalities<sup>6</sup>. MRI may demonstrate high signal changes in the caudate/putamen. The clinicopathological features of sCJD are influenced by variations in *PRNP*. The duration of illness to death is typically less than 6 months. In comparison, vCJD more commonly occurs in a younger

population (median age at death 28 years), is associated with early psychiatric symptoms (depression, anxiety, apathy, delusions), sensory disturbances, longer duration of illness and bilateral symmetric pulvinar high signal on MRI brain, without the typical EEG findings of sCJD. Genetic forms of CJD can only be reliably distinguished by the presence of sequence variations of *PRNP*<sup>1</sup>. Iatrogenic forms are classified on the basis of CJD in a recipient of human cadaveric-derived pituitary hormone or with a recognized exposure risk, e.g. antecedent neurosurgery with dura mater implantation.

FFI and sFI present with insomnia and altered sleep, in association with myoclonus, ataxia, dysarthria, dysphagia, pyramidal signs and autonomic hyperactivation, and result from involvement primarily of the thalamus. GSS is characterized by an early onset (between 30 and 60 years of age), and slow disease progression extended over a period of 3.5-9.5 years. Clinical symptoms, which may show intra-familial and intra-generational variation, include cerebellar ataxia, gait abnormalities, dementia, dysarthria, ocular dysmetria, infrequent myoclonus, spastic paraparesis, parkinsonian signs, and hyporeflexia or areflexia in the lower extremities. Kuru may have a prodrome of headache and joint pain, followed by 3 clinical stages: ambulant (still can walk), sedentary (only can sit up), and terminal (unable to sit up independently). Cerebellar ataxia, tremors and choreiform and athetoid movements are distinctive and prominent clinical signs. Shivering amplifiable by cold was the symptom on the basis of which the disease was named “kuru”. A dementing illness, as is prominent in sCJD, can also occur in some cases, but happens during the final disease stages only<sup>2</sup>. VPSPr was initially described in people with atypical dementia. The clinical course is often up to 2 years, longer than sCJD.

**CJD, including vCJD, is a notifiable disease within Australia to the relevant state or territory health department communicable disease control unit. Notification is indicated where a strong CLINICAL SUSPICION for CJD exists.**

In addition, the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) is under contract to the Commonwealth for national surveillance of human TSEs and provides diagnostic testing services to aid in the assessment of all suspected cases of human TSEs, including CJD, within Australia (Florey Institute of Neurosciences and Mental Health, The University of Melbourne, Kenneth Myer Building, 30 Royal Parade, Gate 11 Rear Loading Dock, Parkville, Victoria 3010 Australia, ph 03 83441949, fax 03 93495105, email ANCJDR (ancjd-reg@unimelb.edu.au)), however notification to state and territory health department communicable disease control units is still required.

## 3 Tests

**The only laboratory method for making a definite diagnosis of TSE is histopathological examination of brain tissue.**

### 3.1 Histopathological examination

#### 3.1.1 Brain Biopsy

A definite diagnosis of TSE, including CJD and vCJD, is established only by neuropathological examination. Autopsy, or at least post-mortem brain biopsy, is strongly encouraged in any suspected case of human TSE. Ante-mortem brain biopsy typically involves the removal of a small piece of non-dominant frontal cortex, and is generally only recommended when the clinical features are atypical and the diagnosis of an alternative treatable disease is being sought. Although usually diagnostic in

CJD, approximately 5% of biopsies from subsequently confirmed definite cases are non-diagnostic, reflecting “sampling error” from the variable distribution of brain pathology in CJD. The extent and intensity of pathological features increase as the disease progresses and therefore, the pathological characteristics become more marked in patients with a disease of long duration<sup>4</sup>.

The sporadic, genetic and iatrogenic forms of CJD and VPRPr characteristically display neuropathological findings of spongiform lesions, reactive astrocytosis and neuronal loss in the cerebral and/or cerebellar cortex and/or subcortical grey matter, with accumulation of the abnormal prion protein (PrP<sup>Sc</sup>), demonstrated by immunohistochemistry or immunochemical detection by immunoblot; however, lesion profiles may vary depending on the molecular sub-type.

The neuropathology of vCJD is distinctively different from sCJD. In particular, a large number of PrP amyloid plaques surrounded by a halo of spongiform change (‘florid plaques’ or ‘daisy-like’ plaques) are seen, particularly in the cerebral and cerebellar cortical grey matter<sup>1</sup>. The ‘florid plaques’ are not specific for vCJD (also may be seen in gCJD) but their widespread distribution is characteristic of the disease. Amorphous pericellular and perivascular PrP<sup>Sc</sup> deposits, especially prominent in the cerebellar molecular layer, and multiple small PrP<sup>Sc</sup> plaques which are only detectable by immunohistochemical staining, may also be present. In addition to amyloid plaques, vCJD displays some other neuropathological features that make it distinguishable from other human prion diseases. Posterior thalamic astrocytic gliosis is more extensive in vCJD than in other forms of the disease (i.e. the total number of astrocytes is higher in vCJD than in sCJD). This severe astrocytic gliosis is accompanied by marked neuronal loss in vCJD<sup>1</sup>.

Pathological changes are more anatomically restricted in FFI and sFI, with neuronal loss and astrocytic gliosis occurring predominantly in the thalamic nuclei and the inferior olives, with scant PrP deposition<sup>2</sup>. In general, the neuropathologic features of GSS patients include thalamic degeneration and severe to absent spongiform changes in the cerebrum, with numerous amyloid plaques, neuronal loss, astrocytic microgliosis, and variable neurofibrillary tangles<sup>2,3</sup>. The neuropathological property which distinguishes kuru from sCJD is the presence of numerous kuru plaques: spherical bodies with a rim of radiating filaments.

Specialist neuropathology referral centres are available for examination of histopathological specimens from suspected TSE cases for each Australian state and territory according to Table 1.

**Table 1: Neuropathology Referral Centres for Suspected TSE, including CJD and vCJD**

State/Territory	Autopsy Service	Histopathology Service
VIC/TAS/SA/NT	Alfred Hospital Mortuary	Neuropathology Histology Laboratory, The Florey Institute of Neuroscience and Mental Health
NSW/ACT	Department of Forensic Medicine, Glebe	Department of Neuropathology, Royal Prince Alfred Hospital
QLD	Royal Brisbane & Women’s Hospital Mortuary	Anatomical Pathology, Pathology Queensland Royal Brisbane Hospital Campus
WA	PathWest Laboratory Medicine Royal Perth Hospital	Section of Neuropathology, PathWest Laboratory Medicine Royal Perth Hospital

### 3.1.2 Lymphoreticular Tissue Biopsy (vCJD only)

PrPsc deposition in the germinal centres of lymphoid tissues (including tonsils, appendix, spleen and lymph nodes) has been identified in neuropathologically confirmed cases of vCJD, but not in small cases series of sCJD, iCJD and gCJD<sup>7</sup>.

Various lymphoreticular tissues can be utilized, but tonsils are by far the best candidate due to the large number of germinal centres<sup>1</sup>. If tonsils are not available, the next best candidate is spleen tissue; if spleen is unavailable, then peripheral lymph nodes can be sampled in which case, multiple sampling is necessary in order to increase the chances of detecting PrPsc. In this situation an extremely careful examination is required, since the germinal centres of lymph nodes are small. Some additional frozen material should always be saved for immunoblot examination; an immunoblot negative for PrPsc will be useful to confirm a negative immunohistochemistry finding, and can also rule out a false positive due to incomplete removal of PrPc.

On the basis of the published data, tonsil biopsy cannot be recommended as a routine diagnostic procedure in the investigation of vCJD. Tonsil biopsy may however have a role in the classification of probable vCJD in suspect cases where clinical features are compatible with vCJD but MRI does not show typical changes (bilateral pulvinar high signal)<sup>6,3</sup>.

The finding of negative lymphatic tissues cannot exclude the diagnosis of vCJD, but if multiple large samples are all negative, then the likelihood of vCJD is considerably reduced.

## 3.2 CSF examination

### 3.2.1 14-3-3 protein by immunoblot and total Tau protein by ELISA in CSF

The cerebrospinal fluid (CSF) of patients with TSE typically contains no inflammatory cells. A slightly elevated protein (0.5-1.0g/L) occurs in about one-third of cases. The presence of oligoclonal bands confined to the CSF has only very rarely been described.

The 14-3-3 protein in CSF has been examined as a laboratory marker of CJD. 14-3-3 is a neuronal protein involved in cell signaling and is present in high concentrations within the central nervous system. It may be released into the CSF following neuronal injury or death. Therefore, its presence in the CSF is not specific for CJD. False positives are recognized in various disease processes, including herpes simplex and other viral encephalitides, recent stroke, sub-arachnoid haemorrhage, hypoxic brain damage, metabolic encephalopathy after barbiturate intoxication, glioblastoma, carcinomatous meningitis from small-cell lung cancer, paraneoplastic encephalopathy and corticobasal degeneration<sup>4</sup>. However, in the appropriate clinical context, the detection of 14-3-3 in the cerebrospinal fluid (CSF) has a high degree of sensitivity and specificity for the diagnosis of sCJD<sup>6</sup>. Results show that this test can be positive even in the early stages of the clinical disease and, in an experimental animal TSE in a primate, in the pre-symptomatic phase as well.

As there is no difference between the electrophoretic pattern of the CSF 14-3-3 found in vCJD and that found in sCJD (although lower concentrations tend to be found in vCJD), CSF 14-3-3 cannot be used to distinguish between the two forms. This is particularly relevant as CJD is the main differential diagnosis of vCJD<sup>4</sup>.

Similar to 14-3-3 protein, total tau protein in CSF is a non-specific marker of neuronal injury which may complement 14-3-3 protein detection for supporting the diagnosis of sporadic CJD<sup>10</sup>. Total tau is not included in diagnostic criteria and there is no internationally agreed cut-off for positives. It may also occur with encephalitis, encephalopathies and cerebral infarction<sup>9</sup>

Analysis of CSF for 14-3-3 protein and t-tau protein requires specialized technical and interpretative skills. In Australia, diagnostic testing is available at the Australian National CJD Registry, Florey Institute of Neurosciences and Mental Health, The University of Melbourne (ANCJDR).

### 3.2.3 Real Time Quaking Induced Conversion (RT-QuIC) in CSF

RT-QuIC exploits the ability of PrP<sup>sc</sup> to induce PrP<sup>c</sup> to misfold.<sup>8,11,12</sup>. Second generation assays utilize recombinant prion protein (recPrP) as substrate to form PrP<sup>sc</sup> aggregates in the presence of very small amounts of PrP<sup>sc</sup> in CSF. Detection occurs through binding to a fluorescent dye (thioflavin). Second generation assays typically take <30 hours. RT-QuIC is less useful for detection of vCJD.

There is no reliable blood RT-QuIC assay due to issues with inhibition. Studies have assessed RT-QuIC testing of olfactory neuroepithelium nasal brushes and skin samples, however these are not routinely available.

RT-QuIC is currently only available at the ANCJDR on a research only basis on discussion with the clinician<sup>12</sup>.

### 3.3 Genetic Analysis

Approximately 10-14% of human TSEs occurs due to an inherited mutation, occurring in one in ten million people<sup>9,13</sup>.

Screening cases of CJD for the mutations associated with the hereditary forms of disease raises significant medical, ethical, psychological, and legal issues for all living blood relatives. Consultation with a specialist clinician or a clinical genetics service is strongly recommended to ensure that the requesting individual/family fully understand/s the test procedure, benefits, limitations and the possible consequence of the test result<sup>9</sup>. Due to the low PrP gene mutation detection rate in 'sporadic' CJD PRNP screening is not routinely recommended in those patients without a family history of a TSE<sup>4</sup>.

In genetic prion disease, the definitive test is the analysis of *PRNP* (the prion protein gene) on chromosome 20 for relevant mutations. This test can be performed on blood or unfixed brain tissue.

Genetic analysis also allows for the determination of the *PRNP* codon 129 genotype (MM, VV or MV). This has potential relevance in the full characterisation of a case of prion disease. Over 70% of cases of sCJD have the MM genotype but the disease does occur in the other two genotypes. Until a recent report of MV genotype<sup>14</sup>, vCJD (defined as definite or probable on the current agreed diagnostic criteria) had only occurred as a MM genotype<sup>6</sup>.

*PRNP* testing, including codon 129 analysis, on blood and tissue specimens from *symptomatic* or *deceased* patients is available at the Neurogenetics Unit, Department of Diagnostic Genomics, PathWest Laboratory Medicine WA, Level 2 PP Building, QEII Medical Centre, Hospital Avenue, Nedlands WA 6009, phone 08 6383 4219.

Testing is not provided for individuals who are **not** experiencing symptoms of CJD, but who are concerned about their own risk for genetic CJD. In these situations, all individuals are able to access testing through the local genetic counselling services as per [HGSA guidelines for Pre-symptomatic and Predictive Testing for Genetic Disorders](http://www.hgsa.org.au/documents/item/1574) (www.hgsa.org.au/documents/item/1574).

### 3.4 Quality Assurance

- *Suitable and Unsuitable specimens*

Autopsy, or at least post-mortem brain biopsy, is strongly encouraged in any suspected case of CJD. Ante-mortem brain biopsy typically involves the removal of a small piece of non-dominant frontal cortex, and is generally only recommended when the clinical features are atypical and the diagnosis of an alternative treatable disease is being sought. **Due to its biophysical properties, including the typical protease resistance, PrP<sup>sc</sup> resists chemical and physical sterilization; hence, prior to ante-mortem or post-mortem tissue biopsy or autopsy, the local Infection Prevention and Control Unit and pathology service should be notified to ensure appropriate procedures are undertaken in the operating theatre around destruction or quarantining of surgical instruments, with re-processing of surgical instruments only if CJD negative, and within the laboratory and mortuary with regards handling of the specimen and body.** Reference should be made to local and national guidelines<sup>15</sup>.



For 14-3-3 and t-tau protein analysis, CSF samples of no less than 1mL of UNSPUN CSF should be packaged in polypropylene, sterile tubes without additives and transported frozen on dry ice, along with results of routine cell counts and protein levels. ANCJDR staff should be notified that the sample is being sent<sup>9</sup>. Unsuitable specimens include: (1) macroscopically haemorrhagic samples and those with red blood cell counts > 500 cells per  $\mu$ L, (2) xanthochromic samples, (3) white cell counts >10 cells per  $\mu$ L or (4) spun supernatants. These samples are unsuitable to test due to the 14-3-3 protein existing in erythrocytes, platelets and plasma. Lysis of these cells releases the protein thus contaminating the CSF sample and giving a false positive result.

Tonsillar biopsy testing for vCJD involves testing a sample of tonsil (fresh and fixed) tissue for evidence of PrPSc. Contact the ANCJDR **before** collecting tissue biopsies for instructions and requirements<sup>9</sup>. **Due to its biophysical properties, including the typical protease resistance, PrPsc resists chemical and physical sterilization; hence, prior to tissue biopsy, the local Infection Prevention and Control unit and pathology service should be notified to ensure appropriate procedures are undertaken in the operating theatre around destruction or quarantining of surgical instruments, with re-processing of surgical instruments only if CJD negative and within the laboratory with regards handling of the specimen.** Reference should be made to local and national guidelines<sup>15</sup>.

Genetic testing for CJD - blood samples can be collected from patients suspected or diagnosed with clinical CJD and stored long-term at the Neurogenetics Unit, Department of Diagnostic Genomics, PathWest Laboratory Medicine WA, Level 2 PP Building, QEII Medical Centre, Hospital Avenue, Nedlands WA 6009, phone 08 6383 4219. Samples from autopsy tissues may also be used for *PRNP* testing. *PRNP* testing is not undertaken on available samples unless documented consent has been provided, organised by the requesting doctor or Genetic Counselling service. In addition, codon 129 testing from tissue or blood samples can be performed if vCJD is suspected.

- *Test Sensitivity and specificity*

Approximately 5% of brain biopsies from subsequently confirmed definite cases of CJD are non-diagnostic, reflecting the variable distribution of neuropathology. The extent and intensity of pathological features increase as the disease progresses and therefore, the pathological characteristics become more marked in patients with a disease of long duration<sup>4</sup>.

An evaluation of all 2002-2008 Australian CSF referrals for 14-3-3 protein analysis, where there was a known clinical outcome, revealed a test sensitivity of 88.5% and specificity of 87.6%. Unselected sampling is less reliable and the 14-3-3 protein CSF test is not recommended as a screen for a possible diagnosis of CJD<sup>9</sup>.

CSF 14-3-3 protein is less sensitive in the diagnosis of vCJD than sCJD. For example, in the UK CJD Surveillance Unit, the sensitivity of CSF 14-3-3 detection in the diagnosis of vCJD has been reported to be between 50-60% and its specificity appears to be up to 94%<sup>1</sup>. There is evidence to suggest that a positive CSF 14-3-3 is more likely to be found in the mid-stage of the disease for vCJD; however this finding should not be used to determine the timing of lumbar puncture as CSF 14-3-3 has been detected at all points in the disease process. Results from patients with genetic TSE have been somewhat mixed, with a positive CSF 14-3-3 protein result in only 50% of a group of 10 genetic cases

with various point mutations, but all of a series of 16 CJD cases related to the codon 200 (E200K) mutation. Most cases of iCJD test positive for CSF 14-3-3 protein<sup>4</sup>.

Sensitivity and specificity of t-tau protein for sCJD ranges from 85-89% and 82-88% respectively<sup>9,16,17</sup>. Sensitivity varies depending on the subtype of sCJD<sup>16</sup>.

Sensitivity and specificity of RT-QuIC for sCJD ranges from 70-96% and 98-100% respectively. It has been shown superior in the diagnosis of sCJD when compared to 14-3-3 and t-tau proteins<sup>11,12</sup>. RT-QuIC responses are inhibited by blood contamination. CSF protein >1g/L and/or elevation in CSF white cell count may result in false positives. There is less information regarding performance for gCJD. The sensitivity was 67% for iCJD secondary to use of cadaveric growth hormone<sup>12</sup>.

## 4. Agreed Typing & Subtyping Methods

### 4.1 Laboratory Nomenclature for National Database Dictionary

Molecular typing of sporadic CJD is performed by the ANCJDR. There are at least six major subtypes based on *PRNP* codon 129 genotype (homozygous methionine MM, homozygous valine VV and heterozygous MV) and type of PrPsc accumulating in the brain (type 1 or 2) that are significantly related to distinctive clinical-pathological subgroups of disease<sup>11,17</sup>.

## 5 Snomed-CT Terminology

SNOMED CT concept	Code
Creutzfeldt-Jakob agent (organism)	88520007
Prion (organism)	84676004
Creutzfeldt-Jakob disease (disorder)	792004
Variant Creutzfeldt-Jakob disease (disorder)	304603007
14-3-3 protein (substance)	430834001
Measurement of 14-3-3 protein concentration in cerebrospinal fluid (procedure)	430834001

## 6 References

1. The Revision of the Surveillance Case Definition for Variant Creutzfeldt-Jakob Disease (vCJD); Report of a WHO consultation, Edinburgh, United Kingdom 17 May 001. World Health Organization. Department of Communicable Disease, Surveillance and Response. Accessed on 12 August 2015. ([libdoc.who.int/hq/2002/WHO\\_CDS\\_CSR\\_EPH\\_2001.5.pdf](http://libdoc.who.int/hq/2002/WHO_CDS_CSR_EPH_2001.5.pdf)).
2. Imran M, Mahmood S. An overview of human prion diseases. *Virology Journal*. 2011;8:559.
3. WHO manual for surveillance of human transmissible spongiform encephalopathies including variant Creutzfeldt-Jakob disease. 2003. World Health Organization. Department of Communicable Disease, Surveillance and Response. Accessed 12 August 2015. ([whqlibdoc.who.int/publications/2003/9241545887.pdf](http://whqlibdoc.who.int/publications/2003/9241545887.pdf)).
4. [Global Surveillance, Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a WHO Consultation, Geneva, Switzerland, 9-11 February 1998. World Health Organization, Department of Emerging and other Communicable Diseases, Surveillance and Control](#). Accessed on 12 August 2015. ([www.who.int/csr/resources/publications/bse/WHO EMC\\_ZDI\\_98\\_9/en/](http://www.who.int/csr/resources/publications/bse/WHO EMC_ZDI_98_9/en/)).
5. Gill ON, Spencer Y, Richard-Leondt A et al. Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. *BMJ* 2013;347:f5675.
6. Investigations undertaken in possible cases of human prion disease. 2012. The National CJD Research and Surveillance Unit, University of Edinburgh. Accessed on 12 August 2015. ([www.cjd.ed.ac.uk/diagnosis](http://www.cjd.ed.ac.uk/diagnosis)).
7. Will RG, Zeidler M, Stewart GE, Macleod MA, Ironside JW, Cousens SN, Mackenzie J, Estibeiro K, Green AJ, Knight RS. Diagnosis of new variant Creutzfeldt-Jakob disease. *Ann Neurol*. 2000;47:575-82.
8. Atarashi R, Satoh K, Sano K, Fuse T, et al. Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion. *Nature Medicine*. 2011;17:175-178.
9. [Australian National Creutzfeldt-Jakob Disease Registry \(ANCJDR\), Florey Institute](#). Accessed 8 February 2020. ([www.florey.edu.au/science-research/scientific-services-facilities/australian-national-cjd-registry](http://www.florey.edu.au/science-research/scientific-services-facilities/australian-national-cjd-registry)).
10. Li Q-X, Varghese S, Savios S et al. CSF tau supplements 14-3-3 protein detection for sporadic CJD diagnosis while transitioning to next generation diagnosis. *J Clin Neuroscience*. 2018;50:292-293.
11. Foutz A, Appleby BS, Hamlin C, Liu X et al. Diagnostic and prognostic value of human prion detection in cerebrospinal fluid. *Ann Neurol* 2017;81:79-92.
12. Green AJE. RT-QuIC: a new test for sporadic CJD. *Pract Neurol* 2019;19:49-55.
13. Minikel EV, Vallabh SM, Leli M, Estrada K et al. Quantifying prion disease penetrance using large population control cohorts. *Science Translational Med*. 2016;8(322):322ra9
14. Mok T, Jaunmuktane Z, Jorner S et al. Variant Creutzfeldt-Jakob disease in a patient with heterozygosity at *PRNP* codon 129. *NEJM*. 2017;376.

15. [The Creutzfeldt-Jakob Disease. January 2013. Infection Control Guidelines. Australian Government. Department of Health.](#) Accessed on 8 February 2020.  
([www.health.gov.au/internet/main/publishing.nsf/Content/icg-guidelines-index.htm](http://www.health.gov.au/internet/main/publishing.nsf/Content/icg-guidelines-index.htm)).
16. Lattanzio F, Abu-Rumeileh S, Franceschini A, Kai H et al. Prion-specific and surrogate CSF biomarkers in Creutzfeldt-Jakob disease: diagnostic accuracy in relation to molecular subtypes and analysis of neuropathological correlates of p-tau and A $\beta$ 42 levels. *Acta Neuropathol* 2017;133:559-578.
17. Parchi P, Strammiello R, Giese A, Kretzschmar H. Phenotypic variability of sporadic human prion disease and its molecular basis: past, present, and future. *Acta Neuropathologica* 2011;121:91-112.