

Creutzfeldt-Jakob Disease (CJD) and other Human Prion Diseases

Investigative Guidelines

October 2018

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To detect the emergence of variant Creutzfeldt-Jakob Disease (vCJD, which may indicate that beef from cows with bovine spongiform encephalopathy [BSE; “mad cow disease”] is in the food supply) or novel transmissible spongiform encephalopathies (TSEs) caused by prions.
2. To prevent iatrogenic transmission.
3. To monitor epidemiologic trends in the occurrence of CJD and other TSEs in Oregon.
4. To educate and link families and providers to the CJD Foundation, which supports families affected by prion disease.

1.2 Laboratory and Physician Reporting Requirements

Any suspected CJD, vCJD or other human TSE case should be reported **within one local public health authority working day** to local health departments, or, if they are unreachable, to the Oregon Public Health Division (OPHD).

1.3 Local Health Department Reporting and Follow-Up Responsibilities

Because a confirmed diagnosis of CJD or vCJD requires analysis of brain tissue, it's important to work with the case's primary care provider (PCP), who can encourage their patients or patients' next of kin to consent to an autopsy.

1. Contact PCP to discuss and encourage an autopsy, emphasizing that the only way to confirm the diagnosis is with autopsy tissue, and that the National Prion Disease Pathology Surveillance Center (NPDPSC; 216-368-0587; www.cjdsurveillance.com) will pay for all autopsy-related expenses, including body transportation to Oregon Health & Science University (OHSU). The autopsy consent form (<https://case.edu/medicine/pathology/sites/case.edu.pathology/files/2018-06/NPDPSC-Autopsy-Consent-%282018%29.pdf>) must be completed for the NPDPSC to coordinate the autopsy. After the next of kin consents to autopsy, most of the coordination will happen among the NPDPSC, the funeral home, and OHSU pathology.

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2. Encourage PCP to link family of case to the CJD Foundation (www.cjdfoundation.org)
3. If the case is <55 years old, concern for vCJD is higher; additional risk-related information will need to be entered into Orpheus, and pertinent sections of the medical record will need to be redacted and sent to CDC's prion surveillance program within two weeks of report date.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

The causative agents of TSEs are believed to be prions, which are abnormally folded versions of proteins normally present in the brain. They are “transmissible” insofar as they are able to induce abnormal folding of normally folded analogous proteins. The term “prion” is derived from the phrase “proteinaceous infectious particle.” The functions of the normally folded prion proteins (PrPs) are not completely understood. The abnormal folding of the prion proteins leads to brain damage that, grossly, appears “spongiform,” and to the characteristic signs and symptoms of the disease. **Prions are resistant to routine physical and chemical sterilization measures.** Destruction is the safest and most unambiguous method of handling heat-resistant surgical instruments that come in contact with high-infectivity tissues; but stringent chemical and autoclave sterilization methods (found at www.cdc.gov/prions/cjd/infection-control.html) may also be used. Human prion diseases include Creutzfeldt-Jakob Disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), Gerstmann-Sträussler-Scheinker (GSS) Syndrome, Fatal Familial Insomnia (FFI), Sporadic Fatal Insomnia (sFI), and Kuru. Distinguishing features of selected human prion diseases are listed in Table 1.

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Table 1. Distinguishing features of selected human prion diseases

Form	Cause	Distinguishing Features
Sporadic CJD	Unknown	Affects mainly >60-yr-olds. Common symptoms include ataxia and dementia. Short course. Brain tissue shows spongiform change, but plaques are rarely present.
Sporadic Fatal Insomnia (sFI)	Unknown	Behavioral or mood changes, ataxia, and sleep disturbances, which can be further evaluated by polysomnography and positron emission tomography (PET) testing.
Inherited Prion Disease Familial CJD	Inherited mutation in PrP gene	Often younger onset than sCJD. Symptom pattern depends on type of mutation, but can be similar to sporadic. Course of illness usually longer.
Acquired CJD	Exposure through brain surgery, corneal transplant, dura mater graft, or transmission from exposure through a peripheral route (as with human growth hormone [hGH] injections)	Age at onset depends on the age at exposure and on the incubation time. Clinical and pathological features are often indistinguishable from sCJD. Growth hormone cases show plaques.
Variant (vCJD)	Exposure to bovine spongiform encephalopathy (BSE) through consumption of infected beef or blood or plasma transfusion	Younger onset and longer duration than sporadic CJD. Psychiatric symptoms often seen at disease presentation. Distinctive “daisy” plaques in brain tissue. For blood and plasma transfusion, age at onset depends on the time of exposure.

2.2 Description of Illness

Prion diseases are progressive and always fatal. They typically have decades-long incubation periods and cause characteristic spongiform changes in the brain, neuronal loss and gliosis *without* provoking an inflammatory reaction. Death usually occurs within a year after onset of illness.

Sporadic CJD occurs worldwide and is the most common human prion disease (estimated incidence: 1–2 cases per million population per year). It is a fatal neurodegenerative disease that occurs primarily in persons >55 years of age. It

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usually begins with cognitive and behavioral changes (e.g., memory difficulties) and progresses to include physical neurologic signs, e.g., myoclonus, ataxia, rigidity. Death is often caused by aspiration or sepsis and usually ensues within one year of onset.

Familial CJD results from inherited mutations in the prion protein gene. Compared to sporadic CJD, patients with familial CJD are generally younger and have a family history of prion disease.

vCJD was recognized in the United Kingdom in the 1990s. Consumption of products from BSE-infected cattle is the likely mode of transmission to humans. In contrast to sporadic CJD, vCJD is characterized primarily by behavioral changes (e.g., psychosis, depression), painful sensory symptoms, a younger age of onset (even in the teens & 20s), and a longer duration of illness (Table 2).

From October 1996 to April 2018, 178 cases of vCJD were reported in the United Kingdom of Great Britain and Northern Ireland (United Kingdom), and 49 cases in other countries. Although four cases of vCJD have been reported in the United States, all are thought to have been exposed to the disease outside of the United States. Despite aggressive surveillance since 1996, no vCJD cases have been reported in Oregon.

GSS, FFI, and sFI are extremely rare; one case of FFI and two cases of sFI have been reported in Oregon since 1996.

Animal prion diseases include BSE in cattle, scrapie in sheep, and chronic wasting disease in deer and elk.

Table 2. Clinical and pathologic characteristics distinguishing variant and sporadic CJD

Characteristic	vCJD	sCJD
Median age at death	28 years	68 years
Median duration of illness	13–14 months	4–5 months
Clinical signs and symptoms	Prominent psychiatric or behavioral symptoms; painful dysesthesias; delayed neurologic signs	Dementia; early neurologic signs
Periodic sharp waves on EEG	Absent	Often present
“Pulvinar sign” on MRI*	Present in >75%	Not reported
“Florid plaques” on neuropathology	Present in large numbers	Rare or absent
Accumulation of PrP ^{res} † in immunohistochemical analysis of brain tissue	Marked	Variable

Source: CDC. Creutzfeldt-Jakob disease not related to a common venue—New Jersey, 1995–2004. MMWR 2004;53:392–6. Adapted from Belay E, Schonberger L. Variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. Clin Lab Med 2002;22:849.

2.3 Reservoirs

It is unknown whether a reservoir exists for sporadic CJD.

2.4 Modes of Transmission

Prion diseases of humans are not typically transmitted from person to person.

1. Sporadic CJD. Risk factors for development of “sporadic” CJD are unknown; it may arise *de novo* in unlucky persons.
2. Familial CJD. Approximately 5%–15% of human prion disease is “familial” (i.e., inherited).
3. Iatrogenic CJD. <1% of CJD is contracted through iatrogenic transmission, e.g., acquired during medical procedures from contaminated human-derived pituitary hormones, dura mater grafts, corneal grafts or neurosurgical equipment.
4. Variant CJD. Acquisition of vCJD has been associated with consumption of tissue from cattle with BSE. Food-protection measures have been implemented to prevent the sale for consumption of meat products from suspected or confirmed BSE-infected cattle. Cases of vCJD in the United Kingdom show that

* An abnormal signal in the posterior thalami on T2- and diffusion-weighted images and fluid-attenuated inversion recovery (“FLAIR”) sequences on brain MRI; in the appropriate clinical context, this signal is highly specific for vCJD

† Protease-resistant prion protein

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blood transfusions can transmit this disease. However, other human prion diseases are not known to be transmitted by transfusions.

2.5 Incubation Period

The incubation period for the few prion diseases with known sources (i.e., variant CJD, iatrogenic prion disease) is variable and may be extremely long — years to decades.

2.6 Period of Communicability

TSEs are not communicable directly from person to person.

2.7 Treatment

These diseases are invariably fatal. Supportive care is needed, and medications may be used to control aggressive or agitated behaviors.

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Sporadic CJD — Confirmed Case Definition

Pathologist-confirmed diagnosis after examination of brain tissue using standard neuropathological or immunocytochemical stains; or Western-blot-confirmed protease-resistant PrP^{res}; or presence of scrapie-associated fibrils.

3.2 Sporadic CJD — Presumptive Case Definition

Neuropsychiatric disorder PLUS positive real-time quaking-induced conversion (RT-QuIC) test on cerebrospinal fluid (CSF) or other tissues

OR

Rapidly progressive dementia; AND at least two of the following four clinical features: 1) myoclonus, 2) visual or cerebellar signs, 3) pyramidal or extrapyramidal signs, or 4) akinetic mutism;

AND

A positive result on at least one of the following laboratory tests:

1. Periodic sharp wave complexes seen on EEG during an illness of any duration;
2. A positive 14-3-3 cerebrospinal fluid (CSF) assay in patients with a disease duration of less than 2 years;
3. A positive RT-QuIC test;
4. Magnetic resonance imaging (MRI) showing high-signal abnormalities in the caudate nucleus or putamen on diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR);

AND

The absence of an alternative diagnosis after routine investigation.

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3.3 Sporadic CJD — Suspect Case Definition (*not reportable to Oregon PHD*)

Progressive dementia; AND at least two of the following four clinical features: 1) myoclonus, 2) visual or cerebellar signs, 3) pyramidal or extrapyramidal signs, or 4) akinetic mutism;

AND

ALL of the following:

1. The absence of a positive result for any of the three laboratory tests that would classify a case as “probable” (see tests 1–3 above);
2. Duration of illness less than two years; and
3. The absence of an alternative diagnosis after routine investigation.

3.4 Familial CJD

Definite or probable CJD **plus** definite or probable CJD in a first degree relative; or any neuropsychiatric disorder **plus** disease-specific PrP gene mutation.

3.5 Iatrogenic CJD

Definite or probable CJD plus a recognized risk for medical acquisition — e.g., antecedent receipt of human growth hormone or dura mater implantation.

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3.6 Definite vCJD

- a. Current age or age at death <55 years (a brain autopsy is recommended, however, for all physician-diagnosed CJD cases).
- b. Psychiatric symptoms at illness onset and/or persistent painful sensory symptoms (frank pain and/or dysesthesia).
- c. Dementia, and development ≥ 4 months after illness onset of at least two of the following five neurologic signs: poor coordination, myoclonus, chorea, hyperreflexia, or visual signs. (If persistent painful sensory symptoms exist, ≥ 4 months delay in the development of the neurologic signs is not required).
- d. A normal or an abnormal EEG, but not the diagnostic EEG changes often seen in classic CJD.
- e. Duration of illness of over 6 months.
- f. Routine investigations of the patient do not suggest an alternative, non-CJD diagnosis.
- g. No history of receipt of cadaveric human pituitary growth hormone or a dura mater graft.
- h. No history of CJD in a first degree relative or prion protein gene mutation in the patient.

3.7 Suspected vCJD

Neuropathologic examination of brain tissue is required to confirm a diagnosis of variant CJD. The following confirmatory features should be present.

- a. Numerous widespread kuru-type amyloid plaques surrounded by vacuoles in both the cerebellum and cerebrum – florid plaques.
- b. Spongiform change and extensive prion protein deposition shown by immunohistochemistry throughout the cerebellum and cerebrum.

3.8 All other human prion diseases (Confirmed case definition)

Pathologist-confirmed diagnosis after examination of brain tissue using standard neuropathological or immunocytochemical stains.

3.9 Services Available at the Oregon State Public Health Laboratory

OSPHL does not perform diagnostic testing for prion diseases; however, our goal is to have autopsies performed by the Neuropathology Department at OHSU (503-494-8276) on all potential CJD or vCJD cases. Coordinate with OPHD to arrange

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autopsy; if we are unavailable, call the OHSU operator (503-494-9000) and ask for the on-call autopsy resident. Neuropathologist Dr. Randy Woltjer of OHSU is the primary contact for prion diseases.

4. ROUTINE CASE INVESTIGATION

Cases of suspect, presumptive, and autopsy-confirmed prion disease are identified from three main sources: 1) reports from health care providers; 2) lab reports from the National Prion Disease Pathology Surveillance Center (NPDPSC; the national reference laboratory for prion diseases); and 3) death certificates.

4.1 Attempt to Confirm the Diagnosis

Determine whether the patient is alive or deceased. There is no need to interview the next of kin unless vCJD, iatrogenic CJD, a novel prion disease, or a CJD cluster is suspected.

Interview the provider or review medical records to collect information on the patient's clinical presentation and antemortem test results (see above). See Appendix A for definitions of neurologic terms found on the case report form.

If CJD is diagnosed and the patient is still alive, strongly encourage the provider to discuss with the patient the essential role of autopsy for confirming a diagnosis of CJD. If the next of kin consents to an autopsy, he or she should complete the NPDPSC autopsy consent form (available at <https://case.edu/medicine/pathology/sites/case.edu.pathology/files/2018-06/NPDPSC-Autopsy-Consent-%282018%29.pdf>) send or fax it to the NPDPSC. The NPDPSC will cover all expenses related to the autopsy, including brain-only autopsy, roundtrip transportation to and from OHSU, and testing for CJD and other prion diseases. The NPDPSC performs advanced neuropathological and biochemical diagnostics, including histopathology, immunohistochemistry, Western blot, and prion gene analysis to confirm a diagnosis of prion disease and to distinguish among types (e.g., familial vs. sporadic).

If the patient has died, determine the date of death and whether postmortem samples of brain tissue were collected. Ascertain which laboratory has the tissues and ensure that tissues and any pathology reports are forwarded to OHSU Department of Neuropathology, ATTN: Dr. Randy Woltjer.

4.2 Ascertain Exposures

Complete the questions on the Clinical and Risks Tabs in Orpheus.

5. CONTROLLING FURTHER SPREAD

5.1 Infection Control Recommendations

1. Standard precautions are recommended for hospitalized patients; additional special precautions are necessary during some surgical procedures, including surgery on the brain, spinal cord and posterior eye.

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2. **Surgical procedures: Prions are resistant to routine physical and chemical sterilization measures used in medical facilities.** As a result, surgical equipment, surfaces and other objects in contact with certain tissues, including nervous or posterior eye, of persons with suspected or confirmed prion diseases require special decontamination measures. The brain, spinal cord and posterior eye of patients with prion diseases are considered highly infectious.
If a patient with prion disease requires or had within the past 14 months a surgical procedure or invasive EEG monitoring, contact the facility's infection control division so that appropriate infection control measures can be implemented, if needed. Information about infection control measures related to prion disease is available from CDC (www.cdc.gov/prions/cjd/infection-control.html) and the World Health Organization (WHO; <http://whqlibdoc.who.int/publications/2003/9241545887.pdf> and www.who.int/bloodproducts/tablestissueinfectivity.pdf).
3. **Autopsy:** The WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies should be followed during autopsy of a patient with diagnosed human prion disease. See <http://whqlibdoc.who.int/publications/2003/9241545887.pdf>
4. **Embalming:** Information on Creutzfeldt-Jakob Disease for Funeral Home, Cemetery and Crematory Practitioner can be found at: www.health.ny.gov/professionals/funeral_director/diseases/creutzfeldt-jakob/
5. **Blood, Tissue, or Organ Donation:** Tissues and organs from patients with prion disease should not be donated for transplantation or teaching purposes.‡

5.2 Case Management

If routine case investigation has been completed, no case follow-up is needed after an autopsy is arranged. Once pathology results are available, they will be sent to the patient's physician and to OPHD, which, in turn, will forward them to the local health department, which will be responsible for updating the case record in Orpheus. Using these pathology results, the case can be classified.

5.3 Contact Management

No follow-up is needed for close contacts of the patient since there is no evidence that any human prion disease is transmitted directly from person to person, even with intimate contact. If the patient had a surgical procedure when the hospital was unaware of the disease status, contact the infection control practitioner of the hospital or clinic where the patient had the procedure.

‡ Note: Additional infection control measures are recommended in some circumstances for asymptomatic persons who are at risk for developing prion disease based on any of the following: 1) receipt of dura mater **or** corneal transplants, or human-derived pituitary hormones, especially human-derived growth hormone; 2) history of having undergone neurosurgery; or 3) any known blood relationship to persons with heritable prion disease. Source: World Health Organization Communicable Disease Surveillance and Response. WHO Manual for surveillance of human transmissible spongiform encephalopathies.

6. ROUTINE PREVENTION

6. There is no vaccine against human prion diseases. There are no prevention measures for the majority of human prion diseases. See the infection control WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies should be followed during autopsy of a patient with diagnosed human prion disease. See <http://whqlibdoc.who.int/publications/2003/9241545887.pdf>.

UPDATE LOG

October 2018: Incorporated new diagnostic criterion, the RT-QuIC test, for determining case classification of presumptive, sporadic CJD case. (Stephen Ladd-Wilson)

June 2017. Added reference to CJD Foundation; added case definitions for iatrogenic, familial, and vCJD. (Stephen Ladd-Wilson)

May 2016: updated vCJD numbers and corrected typos. (Stephen Ladd-Wilson)

March 2016. The legal reporting requirement reflect the 2011 revision to the Reportable Diseases Rule case definitions were updated in 2015 due to revision to the national case definitions (http://arcweb.sos.state.or.us/pages/rules/oars_300/oar_333/333_018.htm). (Stephen Ladd-Wilson)

Appendix A — Definitions of neurologic terms found on the case report form

The following terms and their definitions may assist with the questions on the prion disease case-report form and terms that you may find during Creutzfeldt-Jakob Disease (CJD) chart reviews.

Akinetic mutism: the loss of the voluntary ability to speak and move. This term should be specifically stated. Unless it is clearly stated that the patient is awake and not comatose, do not substitute the term “unresponsive.”

Cerebellar signs of CJD may include:

- Ataxia: Failure of muscular coordination. Affected patients have problems with coordination, balance and maintaining posture early in the disease, and, as the disease progresses, severe ataxia leading to loss of ability to walk.
- Opsoclonus: horizontal and vertical oscillations of the eyes
- Nystagmus: involuntary, rapid, rhythmic movement of the eyeball
- Truncal titubation or truncal ataxia: staggering, stumbling gait with shaking of the trunk
- Appendicular ataxia: lack of coordination in a limb
- Movement tremor: involuntary trembling or quivering
- “Termination” or “terminal tremor” would be included in CJD signs; however, “tremor” alone is not necessarily a sign of cerebellar problems or CJD.

Chorea: Writhing movements of the limbs that appear to be well coordinated but occur involuntarily.

Dementia: cognitive decline.

Dysesthesia and painful sensory symptoms: New onset of pain or other uncomfortable sensations unrelated to injury or stimulus.

Dystonia: Abnormal tonicity in muscles resulting in impairment of voluntary movement.

Extrapyramidal signs refer to disorders of brain structures controlling movement, mainly with reference to the basal ganglia and related structures. The most commonly recognized extrapyramidal signs are those associated with Parkinson’s disease. Extrapyramidal signs of CJD may include:

- Bradykinesia or hypokinesia (slowness of movement)
- Rigidity of limbs or neck
- Tremor
- Hypomimia (flat facies, masked facies, lack of facial expression)
- Postural instability
- Shuffling gait
- Ballismus or hemiballismus (sudden flinging movements of the extremities)
- Chorea or choreoathetosis (writhing movements)

Hyperreflexia: Exaggerated reflexes

Myoclonus: Sudden, involuntary contractions or jerking of a muscle or group of muscles. Terms such as “myoclonic jerks,” “myoclonic jerking,” and “myoclonic activity” are also acceptable. These variants of myoclonus may be mentioned:

- Nocturnal myoclonus
- Facial myoclonus
- Action myoclonus
- Startle myoclonus

Terms such as “twitching,” “tremulousness,” “shaking” and “shakiness” are not equivalent; and the term “clonus” represents a separate neurologic sign.

Progressive Dementia: Ongoing cognitive decline. Unlike the dementia of Alzheimer’s disease, the dementia in CJD patients becomes very pronounced over a short period of time (weeks). **Terms like “delirium,” “altered mental status,” or “unresponsiveness” should not be interpreted as representing progressive dementia, unless there is clear evidence in the chart that the condition has been ongoing for weeks, and that the patient’s cognitive ability is getting progressively worse.**

Progressive neuropsychiatric disorder: Abnormalities in the nervous system and in mental processes. In the variant form of CJD, the first symptoms are psychiatric, and patients experience a progressive neuropsychiatric disorder lasting at least 6 months. In the sporadic form, if neuropsychiatric disorders are present, they usually are concurrent with the physical manifestations of the disease.

Pyramidal signs refer to disorders of the upper motor neuron pathway going from the motor cortex through the brainstem and down to the spinal cord. Pyramidal signs would include findings such as:

- Upper motor neuron weakness
- Hemiplegia (paralysis of one side of the body)
- Spastic (limb) paralysis or paresis
- Hyperreflexia
- Babinski’s sign (upgoing toes)
- Spasticity
- Clonus (alternating muscular contraction and relaxation in rapid succession)

Visual Deficits: The visual abnormalities in CJD most commonly are complex visual disturbances, such as hallucinations or cortical blindness. **Do not count terms such as “blurred vision” or “decreased visual acuity.”** Terms that may be used to describe CJD-associated visual deficits include the following:

- Visual hallucinations
- Hemianopsia (defective vision or blindness in half of the visual field)