Guidelines for *PRNP* genetic testing

I Preamble

The following guidelines are recommended procedures, not regulations. They are recommendations concerning the use of genetic testing for the detection of mutations in the prion protein gene (*PRNP*) and were developed by a committee consisting of representatives of genetic counselling services, genetic testing laboratories, the CJD Support Group Network and the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR).

These recommendations are to be used to protect and assist at-risk individuals and should be therefore freely available to patient families to ensure that they are able to make independent informed decisions. These guidelines are also intended to assist clinicians, clinical geneticists, genetic counsellors, testing laboratories, health departments, ethics committees and lay organisations in caring for patients and their families.

II Background

Prion diseases

Prion diseases are rare and fatal degenerative brain diseases, which in most cases are marked by a rapid progression of symptoms. Prion diseases can affect humans and animals. The best know prion disease in animals is bovine spongiform encephalopathy (BSE). Prion diseases are unique in that they are transmissible and can be genetic.

More detail on the clinical features of CJD and how it can be transmitted is provided in appendix 1.

Human prion diseases include:

- **Sporadic** CJD (sCJD) – 85% to 90% of all cases. Sporadic means that the condition is neither inherited nor due to transmission from another person. Family members of people who have had sporadic CJD are not at increased risk of developing CJD.

- **Acquired** forms of prion diseases

Iatrogenic or medically acquired CJD (iCJD)- a very rare condition, iCJD is an acquired form of disease due to transmission via medical treatments or surgical procedures.

Kuru- a prion disease affecting the Fore people of Papua New Guinea that was instrumental in establishing that prion diseases are transmissible. In the 1960s it was found that Kuru was largely transmitted through cannibalism.

Variant CJD (vCJD)- Variant CJD was first reported in 1996 in UK. There have been 230 cases as of 2016, mainly in the UK, as a result of the consumption of BSE contaminated meat products. It is now known that vCJD can be transmitted through blood and blood products. Variant CJD is typically quite different from iCJD and genetic CJD. It generally has a longer

duration of illness and affects, currently, a much younger age group (median age 28 years). Variant CJD is often incorrectly referred to as 'mad cow disease'. There have been no identified cases of variant CJD in Australia.

- **Inherited** forms of prion diseases (10% to 15% of cases)

Familial CJD (fCJD)
Gerstmann-Sträussler Scheinker Syndrome (GSS)
Fatal familial insomnia (FFI)

Inherited prion diseases

Approximately 10-15% of prion disease occurs due to an inherited genetic fault (mutation). Mutations in a gene called the prion protein gene (*PRNP*) can lead to Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). Approximately one in 50,000 people have such a *PRNP* mutation.

There are approximately 23,000 pairs of genes in each cell of the body. One in each pair is inherited from each of our parents. Genes instruct the body to make proteins; the *PRNP* gene instructs the body to make a protein called the prion protein. If a person has a fault (mutation) in *PRNP* there is a 50-50 chance for each child to also have the gene fault and a 50-50 chance that they will inherit the healthy copy of the gene and therefore not be at risk of inherited prion disease.

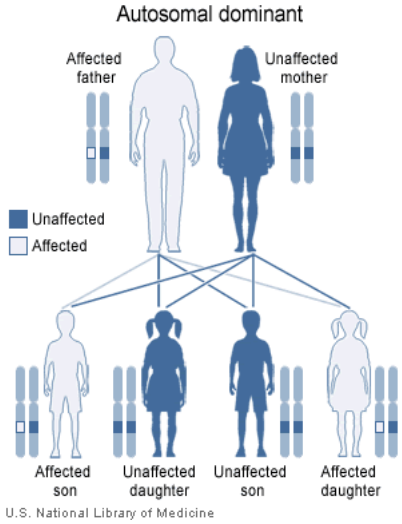

Figure 1- Diagram illustrating autosomal dominant inheritance

There have been multiple different *PRNP* mutations identified to date. In addition there have been many alterations in the chemical sequence of *PRNP* that are rare or uncommon benign variants (so called polymorphisms). Such benign variants do NOT cause prion disease. The risk of whether or not a person will develop symptoms of prion disease from each *PRNP* gene mutation differs and the assistance from persons skilled in genetic counselling and with knowledge in the significance of specific *PRNP* alterations is strongly recommended when such findings are uncovered. With some alterations there is a very high risk that the individual will at some point develop symptoms of prion disease as long as

they live to an old enough age, whereas for others the risk is lower than this, with some members of the family with the familial *PRNP* mutation developing prion disease and others not. The reasons for some developing prion disease and others not developing prion disease are not fully understood.

One factor that is known to influence occurrence of prion disease is which amino acid is present at position 129 in the prion protein. Proteins are made of building blocks called amino acids. There are two possible amino acids at position 129; methionine or valine. Because we have two copies of the *PRNP* gene there are three possible combinations at position 129; two copies of methionine, two copies of valine or one copy of methionine and one copy of valine. For some forms of familial prion disease, having two copies of either methionine or valine may be associated with an earlier age of onset of illness than having one copy of methionine and one copy of valine. The amino acids present at position 129 can also influence which prion condition that a person gets. With one particular gene fault called p.D178N, if on the same copy of the *PRNP* gene a person has p.D178N and methionine they more often develop FFI, whereas if they have a valine at position 129 they usually develop CJD.

The most common *PRNP* mutations are listed in Appendix 3.

III Guidelines for diagnostic/confirmatory testing of symptomatic or deceased patients

DNA Source

In-life blood sample

Taking a blood sample for long-term storage of DNA and/or future *PRNP* testing is optional.

A blood sample, taken while the patient is alive, preserves a sample of the patient's DNA. This allows the patient's family the option to consider *PRNP* testing of their relative at a later stage. The referring doctor should request DNA storage for possible future genetic testing.

Storage and/or testing for all states:

Neurogenetics Unit
Department of Diagnostic Genomics
PathWest Laboratory Medicine WA
Level 2, PP Building
QEII Medical Centre
Hospital Avenue
Nedlands WA 6009
Phone: +61 8 6383 4219
Fax No.: +61 8 9346 4029
Email: mark.davis@health.wa.gov.au

A fee will usually not apply for DNA extraction and storage but this may vary from state to state. Clarification should be sought at the time of the request.

Sample requirements:
At least 5 mls EDTA blood 'marked for DNA extraction and storage for possible future prion protein gene testing for a patient with suspected CJD or other prion disease'.

Brain tissue from a deceased patient

An autopsy where the brain is examined is voluntary. It can provide a definite diagnosis of whether or not the individual had prion disease.

Unfixed autopsy brain tissue of a deceased patient also preserves a sample of the patient's DNA, which can be used at a later stage for *PRNP* testing. Brain tissue from neuropathology confirmed CJD patients is stored indefinitely at the ANCJDR while the ANCJDR is operating. There is no cost associated with the storage of the brain tissue. DNA extraction from autopsy brain tissue and transfer to the testing laboratory incurs a fee of $ 200.

It is recommended to store extracted DNA from a blood sample for every suspected CJD patient in order to secure the option of future genetic testing for the patient's family. Where there is no known family history of prion disease it is advised to await the confirmation of prion disease by neuropathological analysis before proceeding with the *PRNP* test on the stored DNA.

<u>Consent process</u>

Genetic testing is entirely voluntary. Consent for testing a DNA sample can be revoked prior to completion of the testing process.

Testing for genetic prion disease often raises significant medical, ethical, psychological and legal issues for living blood relatives. In the majority of cases, *PRNP* testing will be consented by a lawful next-of-kin due to cognitive impairment of the patient or because the patient is deceased. It is therefore advised that consent is recorded in a written document. Consultation with a clinical genetics service is recommended in general, especially because of the implications if a mutation is detected in *PRNP*. Secondly, the results of a *PRNP* test are not always straightforward, which often makes them challenging to interpret and explain (II background information on inherited prion disease). Finally, a family history is not always known including through misdiagnosis of previous cases in the family. Therefore, a pathogenic *PRNP* mutation may be found in an individual in the absence of a family history (see background information on inherited prion disease).

PRNP testing is frequently requested when a family history of prion disease or concerns for a genetic basis are raised. These tests are often referred by the treating clinician to confirm the aetiology of the disease (genetic or not) to assist in patient care. In cases where there is no family history it is advisable to defer genetic testing until a neuropathology report is available, if a neuropathological confirmation of prion disease was requested.

Result communication and interpretation

The results of *PRNP* testing are not always straightforward, which makes them challenging to interpret and explain. *PRNP* test results provide details of specific pathogenic mutations, benign polymorphisms and codon 129 variants. The implications of *PRNP* sequence variations (autosomal dominant inheritance pattern and consequences for health care due to infection control ramifications) require specialised guidance for the families involved.

In the context of medical testing, the test result must be provided by the laboratory to the requesting health care professional. NATA regulations require that the *PRNP* test results are communicated by a medical professional. Where possible, the health professional giving the genetic test result should be the same one who provided the pre-test information and counselling. Due to complexity and implications of the genetic *PRNP* results, it is recommended that the request for *PRNP* testing is by a trained specialist (neurologist, geriatrician) or genetic-service.

It is important that the test results are relayed to the family and if a positive result that genetic counselling is encouraged. Regardless of the outcome of the results the family should be offered written confirmation of the *PRNP* result as family members may be required to provide this in the future due to the infection control ramifications that surround prion disease.

Confidentiality of patient information

Health care professionals have an ethical, professional and legal duty to protect patient information.

NPAAC has minimum standards for the retention of genetic test results of 100 years by the testing laboratory. The testing laboratory reports the *PRNP* test result to the requesting doctor only. Blood relatives can request a copy of an existing *PRNP* test result from the testing laboratory through a GP or specialist clinician.

Medico-legal and ethical implications of genetic information

Health insurance is “community rated”, therefore a genetic test result has no implication. A person cannot be refused private health insurance on the basis of present or future health status.

Life insurance companies obtain genetic information by asking questions about individual and family health and may request a test result, if it is believed to be relevant information. Under Australian Law, applicants for life insurance are required to disclose any health or genetic information known by the applicants about themselves or genetic blood relatives.

Genetic information could be potentially used to determine eligibility for certain health services, ie. the use of assisted reproductive technologies.

IV Predictive testing

A person at 50% risk of inheriting a *PRNP* mutation can have a test to know whether or not they have inherited this mutation. This is called a predictive or presymptomatic test. If a person has inherited the familial genetic mutation, then the risk of developing symptoms will depend on the specific *PRNP* gene fault, which also dictates the likely form of prion disease that they will get.

Guidelines

Below are guidelines from the Human Genetics Society of Australasia in relation to predictive testing for adult onset disorders. It is recommended that these guidelines be followed for testing for *PRNP* mutations.

Predictive testing in minors

There is much controversy around testing individuals under the age of 18 years for genetic conditions that have their onset in adulthood. Appended below is the position statement from the Human Genetics Society of Australasia in relation to this. It is recommended that these guidelines should be followed for predictive testing for *PRNP* mutations.

Issues specific to *PRNP* predictive testing

PRNP predictive testing differs to any other genetic conditions in that there is the possibility of transmission of prion disease from an individual who has the genetic form of the condition, as is the case for an individual who has non-genetic (so-called sporadic) prion disease. Therefore, an individual who has inherited a *PRNP* gene fault or who has a relative who has a *PRNP* gene fault and has not been tested, should follow the infection control advice that is recommended for individuals with non-genetic prion disease and is outlined elsewhere in appendix1, point 3.

Predictive testing in the absence of *PRNP* testing on an affected individual

If a person has a deceased family member affected by a prion disease but that family member did not have genetic testing, the individual can have testing of *PRNP*. If a mutation is found then they can be advised about the risk of prion disease based on the specific mutation found. If no mutation is found then they can be reassured that they are very unlikely to develop prion disease. Such a result does not mean others in the family are not at increased risk of prion disease since the affected individual may have had a *PRNP* mutation but the tested individual did not inherit this.

Reproductive options

Where one member of a couple has a *PRNP* mutation there are steps they can take to prevent future generations being at risk of genetic prion disease should they choose to do so.

The first option is prenatal diagnosis. This is generally done by a test called chorionic villus sampling (CVS). In a CVS, a tiny piece of the developing placenta is removed via needle under ultrasound guidance. The DNA in the developing placenta is identical to the DNA in the developing baby. If the *PRNP* gene fault is present, then the couple have the option to end the pregnancy. A CVS has a risk of causing a miscarriage of around 1 in 500.

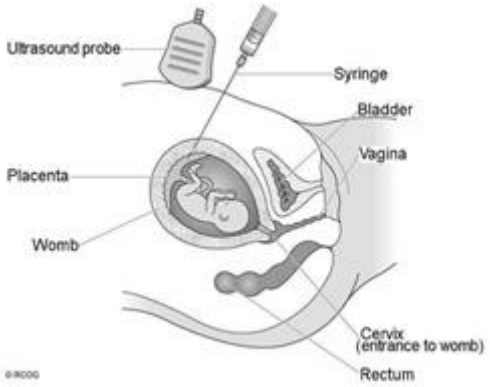

Figure 2- Diagram demonstrating how a CVS is done

It is also possible to use IVF to prevent passing on a *PRNP* gene fault. This is through a process called preimplantation genetic diagnosis (PGD). In PGD, eggs are obtained from the woman and each egg is fertilised with a sperm from the man. The woman has injections of hormones that cause the ovaries to produce multiple eggs. Under a general anaesthetic, eggs are removed using a needle and ultrasound. The single fertilised egg will then divide over and over. After about 5 days there are a 100 or so cells present and a number of these cells are removed. These cells are tested for the *PRNP* gene fault. If the *PRNP* gene fault is present, then that collection of cells, which is called an embryo, is discarded. If the gene fault is not present, then that embryo can be placed in the woman's uterus with the hope of achieving a pregnancy. The single advantage of PGD over prenatal diagnosis is that it largely bypasses the situation where the couple will be faced with a decision whether or not to continue a pregnancy. The issues with PGD are as follows.

1. PGD is not available in all IVF centres.
2. PGD is costly with an out-of-pocket expense of at least $10,000.
3. There is a time requirement for the IVF unit to develop a specific test for each couple that is at least several months.
4. PGD is not as accurate as CVS, so CVS is offered to couples who have had PGD for greater certainty.
5. Although data suggests that the risk of problems to an individual born from the process of IVF and PGD is not high, there are potential concerns about this since it is a relatively new procedure. In addition, there are potential health risks to women having hormone injections as part of IVF.
6. Not all couples achieve a pregnancy using IVF even if fertile naturally.
7. The process of PGD can be stressful particularly if multiple cycles of IVF take place without achieving a pregnancy.

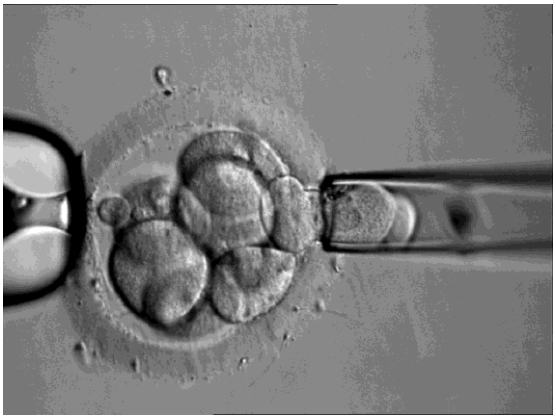

Figure 3- Cells being removed from an embryo that can be tested for a genetic condition such a mutation in *PRNP*

V Genetic counselling services

Genetic counselling services in Australia are listed at http://www.genetics.edu.au/Genetics-Services/genetic-counselling-services

VI Sharing *PRNP* test results with the Australian National Creutzfeldt-Jakob Disease Registry

The Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) was established in 1993. It is based at the Florey Institute of Neuroscience and Mental Health in Melbourne. The ANCJDR is under contract to the Commonwealth Department of Health to perform nationwide surveillance and epidemiology of prion diseases and act as a reference centre to ensure up-to-date surveillance practices and understanding of prion diseases in the health care setting.

When consenting to a PRNP test, families can allow the testing laboratory to share the *PRNP* test result with the ANCJDR to assist surveillance and epidemiological research.

PRNP test results provide information on pathogenic and non-pathogenic alterations in the *PRNP* gene and help the understanding of incidence and distribution of genetic and sporadic CJD in Australia. At the ANCJDR, *PRNP* test results are analysed and reported for CJD surveillance and epidemiology in a coded and de-identified manner. These data help advance the knowledge of prion disease in Australia and worldwide, which may lead to a better understanding of risk factors and prevention of prion disease.

If available, a copy of the *PRNP* result is stored in the patient file for the duration of the ANCJDR's operation. Australian law permits the ANCJDR to provide medical information to close genetic relatives and their treating doctors. This requires written consent and proof of identity and genetic linkage.

The ANCJDR is grateful for the cooperation from families affected by prion diseases; their generosity allows the ANCJDR to collect invaluable information for public health surveillance and epidemiology research.

Appendix 1- Further information about prion diseases, their diagnosis and infection control

1. Prion diseases

Human prion diseases are a rare group of fatal neurodegenerative diseases, which have currently no cure. These diseases include: Creutzfeldt-Jakob disease (CJD), fatal insomnia (FI) which includes sporadic fatal insomnia (sFI) and fatal familial insomnia (FFI) and Gerstmann-Sträussler Scheinker Syndrome (GSS). Clinical features of prion diseases comprise varying combinations of neurologic signs and symptoms including dementia, psychiatric symptoms, incoordination of movements (ataxia, dysarthria), myoclonus (muscle jerks), weakness, spasticity, chorea, seizures, and/or autonomic disturbances. These diseases affect approximately 1 to 2 people in every one million worldwide per year.

The fundamental pathogenic event in prion diseases is believed to be the misfolding of the normal prion protein (PrP^{C}) into an altered conformation (PrP^{Sc}), which accumulates in the brain and causes disease through unresolved mechanisms. The infectious unit of prion diseases known as the "prion" is believed to be composed mostly or entirely of PrPSc. The majority of prion diseases occur on a sporadic basis, which means that no contributing risk factors have been identified so far. A small proportion (10-15% of cases) is attributable to the presence of a mutation in the prion protein gene (*PRNP*).

Prion disease is transmissible from one person to another only through invasive medical procedures by the transfer of contaminated prion protein (PrP^{Sc}). This can be by medical instruments being used for brain or eye surgery later being used for brain or eye surgery on a healthy individual. It can also be transmitted by pituitary hormones being extracted from a person with prion disease and injected into a healthy person. This was the way such hormones, for example growth hormone, were obtained in the past. Since 1985 in most countries, hormones are produced in the laboratory so this should not be a mechanism of transmission into the future. Prion disease is transmissible from anyone with prion disease irrespective of whether their prion disease is sporadic, inherited or iatrogenic. Prion diseases are therefore classified as notifiable diseases, which has implications for carriers of pathological *PRNP* mutations and their genetic (blood) relatives.

Transmission of prion disease DOES NOT occur through routine human contact and is not believed to be sexually transmissible.

2. Diagnosis of prion diseases

When a diagnosis of prion disease is suspected, investigations are undertaken for two broadly separate reasons. Firstly, investigations are used to exclude other possible and/or treatable conditions. Secondly, there are certain investigations which are supportive of a diagnosis of probable prion disease. These include:

- The EEG: in prion diseases the normal electrical rhythms of the EEG are gradually lost and generalised bi- or triphasic periodic sharp wave complexes may appear. The

characteristic periodic pattern is less frequently seen in genetic, iatrogenic or variant prion disease than in sporadic prion disease.

- Tau and 14-3-3 protein analysis: The tau and 14-3-3 proteins are normal neuronal proteins and may be released into the cerebrospinal fluid (CSF) in response to rapid neuronal cell death. A positive 14-3-3 or tau result is supportive of a diagnosis of prion disease but is a non-specific finding and can occur in other illnesses and brain trauma.

- The MRI: Heightened T2 signal abnormalities in the striatum (basal ganglia) and the cerebral cortex are helpful in supporting a diagnosis of prion disease.

An absolutely definite diagnosis of any form of prion disease requires the neuropathological examination of brain tissue but this does not establish whether the patient has sporadic or a genetic form of prion disease. Most commonly the brain is examined after the individual has died but on occasion a brain biopsy is done whilst the person is still alive. The microscopic findings largely specific to prion disease include spongiform degeneration diffusely distributed throughout the cerebral cortex, deep nuclei of the brain and cerebellum, as well as prion protein deposits throughout the brain tissue.

3. Infection control for at-risk individuals

Infection prevention and control standard precautions apply for the care of a patient with suspected CJD or a person at increased risk of developing CJD. It is recommended that all patients undergoing surgical or diagnostic procedures in which higher infectivity tissue will be exposed (e.g. neurosurgery, spinal cord surgery, ophthalmic surgery or pituitary surgery) should have their CJD risk status determined prior to the procedure.

High risk patients

1. Patient who reports neurological symptoms and display neurological signs of prion disease or has been diagnosed with suspected CJD.
2. Family members of a CJD patient who fit into the following categories:

a. An individual has undergone predictive testing and has been confirmed as a carrier of a *PRNP* mutation
b. An individual is from a known genetic family but has not undergone predictive testing to rule out or establish their own risk
c. An individual who has had two or more first or second degree relatives who have died of CJD or other prion disease.

Genetically related members of any family in which there is a strong family history of dementia or neurological illness that are not suggestive of prion disease are classified as **low risk**.

If a person is from a known genetic family and has undergone predictive testing and has a negative result to PRNP testing, then that patient is classified as **background risk** and no special precautions should apply for low or high infectivity tissue. These individuals can also qualify as a blood donor if they fit all other donation criteria.

For more details on infection control issues related to prion diseases please refer to the Australian National CJD Infection Control Guidelines:
http://www.health.gov.au/internet/main/publishing.nsf/content/icg-guidelines-index.htm

Appendix 2- Lay summary sheet

1. The cause of Creutzfeldt-Jakob disease (CJD) in the great majority of patients is unknown and is called Sporadic CJD. Sporadic CJD accounts for 85 to 90% of all cases.

2. A small proportion of cases (10 to 15%) are genetic due to a fault, which is known as a mutation, in the prion protein gene (*PRNP*).

3. Only an examination of the brain tissue, usually performed after death, can confirm or exclude prion disease with certainty. This evaluation does not provide information, however, on whether the patient suffered with a sporadic or genetic form of prion disease. Testing of the patient's *PRNP* gene (diagnostic genetic testing) can establish or exclude a genetic cause for illness.

4. In genetic cases, families may not be aware of a family history of CJD or other prion disease. A family history of CJD or other prion disease may be unknown (for example due to misdiagnosis in previous cases) or may not be present, so the outcome of *PRNP* testing cannot be predicted.

5. If there is a known or suspected family history, in-life diagnostic *PRNP* testing of a suspected CJD patient should be part of the work-up by a specialist.

6. If there is no known/suspected family history of prion disease, the family should be given the option to store DNA (from blood) to secure the option of future *PRNP* testing. It is recommended to await the neuropathology report before proceeding with *PRNP* testing.

7. DNA can also be extracted from autopsy brain tissue in cases where a brain post-mortem has confirmed CJD or other prion disease.

8. It is recommended that a trained specialist (neurologist, geriatrician or geneticist) orders the *PRNP* test and communicates the test result to the family. The referral to the specialist clinicians has to be requested from a GP. In some states a referral is also needed to a genetic service.

9. Families should receive written confirmation of the *PRNP* test result for future reference regardless of the *PRNP* result. This may be needed in the future due to the infection control ramifications for prion disease.

10. In cases where there is a positive result to *PRNP* testing for a mutation, each child of the patient has a 50% chance of inheriting that mutation. This also has implications for siblings of that patient. Predictive testing can determine in a healthy blood relative if he or she has inherited the faulty gene. Each individual has the option to discuss predictive testing (testing of their own DNA) with a genetic service.

11. There are options available to couples, where one has a *PRNP* gene fault, to prevent passing this on to offspring.

12. Family members who inherit a mutation for prion disease are highly likely to develop a genetic prion disease; however, some live to an old age and die of something else first.

13. Establishing that a patient carries a mutation for prion disease does not necessarily confirm that the patient is suffering with, or died of a prion disease. Although highly likely if symptoms and tests all indicate a diagnosis of CJD, a brain only autopsy should still be considered to confirm the diagnosis.

14. In cases where there is a negative result to *PRNP* testing, blood relatives then have the same risk as the general population of developing a prion disease (1 to 2 per million per head of population per year).

15. It is possible that prion disease can be transmitted from a person with any form of prion disease (sporadic, genetic or acquired). This is through exposure to infective tissues such as can occur following surgery on the brain, spinal cord or eyes. If a person has a *PRNP* gene fault or is at high risk of having such a mutation (eg: if a parent has/had such a gene fault) then doctors involved in that person's care should be aware of this so that steps can be taken to minimise the risk of prion diseases being transmitted to another person.

16. Further assistance or advice on who to contact in your area:
CJD Support Group Network (CJDSGN)
Toll free 1800052466 or email: contactus@cjdsupport.org.au

<u>Summary</u>

It is particularly important to know that CJD is not infectious in the way that viruses and bacteria are and there is no risk from routine contact with patients during their illness.

Only a small proportion of cases are genetic.

Storing DNA from a blood sample is voluntary, but secures the option for future genetic testing.

The *PRNP* test is voluntary and requires informed consent of an individual or appropriate family member.

The result of the *PRNP* test will only be made available IF YOU WANT IT TO BE.

The result of the *PRNP* test helps understanding genetic CJD in Australia, if shared with the ANCJDR.

The current cost associated with DNA extraction storage and testing:

- A fee will usually not apply for DNA extraction and storage but this may vary from state to state. Clarification should be sought at the time of the request.
- The current cost of DNA extraction from brain tissue is $200.
- The current cost of *PRNP* testing is $400.
- When a genetic cause is suspected and the test is ordered by the clinician as part of the diagnostic work-up then the cost may be covered by the health system. When the test is consented to through a genetic service the test fee is often covered by the genetic service.

Families should establish if a fee will apply and if any of the above fees will prohibit testing, or cause hardship for the family, the CJDSGN can be contacted for financial assistance with any of the above fees.

Appendix 3- List of the most common PRNP mutations (in Australia)

Mutation	HGVS Nomenclature (used in PRNP report)	Disease phenotype	Lifetime risk of developing illness
Octapeptide repeat inserts (OPRI) (duplications)	Insertion of >one octapeptide repeat segment between codons 51 and 90 -2-3 OPRI -≥4 OPRI	 Uncertain Inherited prion disease	unknown
p.P102L	NM_000311.3:c.305C>T; p.Pro102Leu	GSS	Approaches 100%
p.P105L	NM_000311.3:c.314C>T; p.Pro105Leu	GSS	unknown
p.P105S	NM_000311.3:c.313C>T; p.Pro105Ser	GSS	unknown
p.A117V	NM_000311.3:c.350C>T; p.Ala117Val	GSS	Approaches 100%
p.D178N	NM_000311.3:c.532G>A; p.Asp178Asn with codon 129 Met/Met homozygous)	FFI	Approaches 100 %
p.D178N	NM_000311.3:c.532G>A; p.Asp178Asn with homozygous c. 385 A>G (p. Met129Val)	fCJD	Approaches 100%
p.V180I	NM_000311.3:c.538G>A; p.Val180Ile	fCJD	~1%
p.E200K	NM_000311.3: c.598G>A; p.Glu200Lys	fCJD	Approaches 100 %
p.V210I	NM_000311.3:c.628G>A; p.Val210Ile	fCJD	~9%
p.M232R	NM_000311.3:c.695T>G, p.Met232Arg	fCJD	~0.1%

List of normal (or disease modifying) polymorphisms of PRNP

Codon	
129	Either methionine (Met) or valine (Val) Reported as: Codon 129 is Met/Met homozygous (Methionine/Methionine) Codon 129 is heterozygous, c. 385 A>G (p.Met129Val) (Methionine/Valine) Codon 129 is homozygous c. 385 A>G (p. Met129VAL) (Valine/ Valine)
219	Either glutamate (GAG) or lysine (AAG) Not reported

Appendix 4- Consent form example

REQUEST FOR RELEASE OF PATHOLOGY SAMPLE/DNA AND CONSENT FOR GENETIC TESTING

I,……. (date of birth)……

As next –of-kin of:

Name of patient: ……..

Date of birth: ……..

Date of death *(if applicable):* ……..

request that any tissue/DNA samples pertaining to a diagnosis of Creutzfeld-Jakob Disease are made available to …….. for the purposes of genetic testing of the prion protein gene.

The implications of the testing have been explained to me, and I consent to testing proceeding.

SIGNED:

Signature ……

Name ……

Date ……

CONSENT TO RELEASE GENETIC TEST RESULT

I, ……request that the result of my/my next-of-kin *PRNP* genetic test is made available to the following people/organisations.

- ❑ GP: …….
- ❑ Specialist: ……..
- ❑ Register: ……..
- ❑ Hospital record at ……..
- ❑ Research group ……..
- ❑ Other: ……

I agree that the results may also be used, if necessary, to help other members of my family. Apart from this, my result will be kept completely confidential and will not be released to anyone else without my permission.

Name: ……

Signature: ……

Date of Birth: ……

Date: ……

Literature sourced

Privacy Act 1988 (Cth)
Disability Discrimination Act 1992 (Cwth)
HDSA Genetic Testing Guidelines
Australian National CJD Infection Control Guidelines
NHMRC – Medical Genetic Testing, information for health professionals
NHMRC – Ethical Aspects of Human Genetic Testing, an information paper

Committee members and contact details

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