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... making sense of your genes

Position Statement

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Guidelines for *PRNP* genetic testing

I. PREFACE

The following guidelines are recommended procedures and should be viewed as a framework of recommended procedures, not regulations. The recommendations concern the use of genetic testing for the detection of mutations in the prion protein gene (*PRNP*) and are intended for use by healthcare providers assisting families affected by or suspected to be affected by prion disease and to assist at-risk individuals and those who chose to be tested. These guidelines have been developed by a committee consisting of representatives of clinical genetic services, genetic testing laboratories, the CJD Support Group Network (CJDSGN) and the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR).

Feedback and information from the New Zealand CJD Register, Human Genetics Society of Australasia and Genetic Services is incorporated.

A lay version of the guidelines can be requested directly from the CJDSGN and ANCJDR or downloaded from links below, to ensure that patient families are able to make independent informed decisions.

www.florey.edu.au/science-research/scientific-services-facilities/australian-national-cjd-registry/cjd-diagnostic-tests - PRNP

www.cjdsupport.org.au/site/wp-content/uploads/2019/08/PRNP-Guidelines-final-.pdf

II. BACKGROUND

Prion diseases are rare and fatal degenerative brain diseases, which in most cases are marked by a rapid progression of neurological symptoms and death often occurs within months. Prion diseases can affect humans and animals. Prion diseases are unique in that they are transmissible and can be genetic.

Human prion diseases include sporadic CJD (sCJD), 85–90% of all cases, genetic forms of prion disease, which contribute to 10–15% of cases, and acquired forms of prion disease, including iatrogenic CJD (iCJD), variant CJD (vCJD) and kuru (<1% of all cases).[1] The prevalence of prion disease is estimated at 1–2 cases/million/year.
Whilst the mean onset of prion disease is between the ages of 60–70, the range of age of onset can vary from <20 to >90 years. Genetic cases often have an earlier onset of the illness and on average have a longer illness duration. The early symptoms of prion disease may be subtle and go undetected. Presentations can vary, and early symptoms can include rapid dementia, motor deficits, visual, sleep and/or psychological disturbances.

Genetic prion diseases

Approximately 10–15% of prion disease occurs due to a mutation in a gene called the prion protein gene (*PRNP*). Mutations in *PRNP* can lead to familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). Approximately one in 50,000 people have a pathogenic *PRNP* mutation.[2]

The most common genetic forms of prion disease are inherited in an autosomal dominant pattern. In most cases, an affected person inherits the altered gene from one affected parent. In some people, however, familial forms of prion disease are caused by a new (*de-novo*) mutation in the gene that occurs during the formation of a parent's reproductive cells (germline mutations) or in early embryonic development. Although such people do not have an affected parent and no known family history of prion disease, they can pass the pathogenic mutation to their children.

Families may not be aware of a family history of CJD or another prion disease. A family history of CJD or other prion disease may be unknown (for example due to misdiagnosis in previous generations) or may not be present, so the outcome of *PRNP* testing cannot be predicted. The likelihood that a *PRNP* mutation will be detected in a person with proven prion disease without a known family history of prion disease is approximately 5%.[3]

The sporadic and acquired forms of prion disease are not inherited and do not pose a risk of genetic transmission to family members.

There have been multiple different *PRNP* mutations identified to date. The risk of whether or not a person will develop symptoms of prion disease from a given *PRNP* gene mutation differs; some mutations have a high penetrance (approaching 100%), whereas some mutations only pose a low lifetime risk of developing the illness (down to 0.1%).[3] The reasons for the varying penetrance are not fully understood.

In addition, there are uncommon benign variants of the *PRNP* gene, so-called polymorphisms.[2, 4] A disease modifying polymorphism is present at position 129 (codon 129) in the prion protein. For some forms of genetic prion disease, especially the p.D178N mutation, having two copies of valine is associated with an earlier age of onset of illness than having one copy of methionine and one copy of valine or two methionine alleles. The amino acids present at position 129 can also influence which prion condition a person develops. If a person with p.D178N has a methionine at codon 129 on the same copy of the *PRNP* gene as the p.D178N mutation, they more often develop FFI, whereas if they have a valine at position 129 they usually develop fCJD.

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

A *PRNP* gene test is useful in the following clinical situations:
confirmation/exclusion of a pathological mutation in a suspected or confirmed case of prion disease, predictive testing of an asymptomatic individual known to be at risk of having a pathogenic mutation, and prenatal or pre-implantation testing.

III. GUIDELINES FOR DIAGNOSTIC/CONFIRMATORY TESTING OF SYMPTOMATIC OR DECEASED PATIENTS

III.1 DNA SOURCE

Confirmatory testing by analysis of the *PRNP* gene may be offered at or after the time of the clinical diagnosis of suspected prion disease.

- It is recommended to store extracted DNA from a blood sample for every patient suspected to have a prion disease in order to secure the option of future genetic testing for the patient's family.

- It is preferable to test the symptomatic or deceased patient where possible to avoid unnecessary predictive testing of genetic relatives. That is, if the affected individual is tested and does not have a *PRNP* mutation, then his/her relatives do not need to have testing. If the affected person is not tested, then there may be multiple potentially at-risk relatives who request testing of the *PRNP* gene when there may not have been a causative *PRNP* mutation in the affected individual.

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

- 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 from the patient**.**

- Only sequencing of the patient's *PRNP* gene can establish or exclude a genetic cause for illness with certainty, i.e. delineate between genetic and sporadic prion disease.

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 *PRNP* future genetic testing.**

Storage and/or testing in Australia:

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

Storage and/or testing in New Zealand:
To obtain information about DNA storage facilities in New Zealand please visit:
www.genetichealthservice.org.nz/

DNA storage can be requested by the treating doctor with consent from the patient's next of kin or the person who has medical power of attorney.

Sample requirements:
At least 5 mls EDTA blood

Brain tissue from a deceased patient:
An autopsy, where the brain of a patient suspected to have a prion disease is examined, is voluntary. Only a brain autopsy can provide a definite diagnosis of whether or not the individual had prion disease, however, it cannot determine whether the prion disease was sporadic or genetic. Unfixed autopsy brain tissue of a deceased patient, when available, also preserves a sample of the patient's DNA, which can be used at a later stage for *PRNP* testing (but is less optimal than a blood DNA sample).

Brain tissue storage in Australia:
Brain tissue from most neuropathologically confirmed 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 may incur a fee.

Contact details:
ANCJDR
The Florey Institute of Neuroscience and Mental Health
Ph: 03 8344 1949
Fax: 03 9349 5105
Email: ancjd-reg@unimelb.edu.au

Brain tissue storage in New Zealand:
Storage of frozen brain tissue was commenced in late 2018.
Further information can be obtained from the NZ CJD Register: cjd.registry@otago.ac.nz

III.2 CONSENT PROCESS

- It is advised that consent for DNA storage and testing is recorded in a written document.

- Consultation with a local Clinical Genetic Service is recommended.

- In NZ, *PRNP* sequencing can only be authorised by a clinical geneticist.

Testing for genetic prion disease often raises significant medical, ethical, psychological and legal issues for living blood relatives.[5, 6, 7] In the majority of cases, *PRNP* testing will be consented to by a lawful next-of-kin or medical power of attorney due to cognitive impairment of the patient or because the patient is deceased. It is advised that consent is recorded in a written document – Appendix 4.

Consultation with a local Clinical Genetics Service is recommended, for the following reasons:

- implications for family members if a mutation is detected in *PRNP*

- results of a *PRNP* test are not always straightforward, which often makes them challenging to interpret and explain

- a family history is not always known including through misdiagnosis of previous affected individuals in the family. Therefore, a pathogenic *PRNP* mutation may be found in an individual in the absence of a family history.

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.

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

III.3 RESULT COMMUNICATION AND INTERPRETATION

- In Australia, it is recommended that a trained specialist (neurologist, geriatrician or clinical geneticist) orders the *PRNP* test and communicates the test result to the family.

- The communication of mutation results should include genetic counselling by a Clinical Genetics Service. In NZ, this is mandatory.

- Families should receive written confirmation of the *PRNP* test result for future reference regardless of the *PRNP* result.

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.[6, 7] 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 clinical geneticist).

In NZ, *PRNP* testing can only be authorised by a Clinical Genetics Service and test results communicated by the same.

It is important that the test results are relayed to the family and if a *PRNP* mutation is found, that genetic counselling is encouraged/provided. 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.

In cases where a *PRNP* mutation is identified, each child of the patient has a 50% chance of inheriting that mutation. This also has implications for other genetic relatives of the patient. Predictive testing can determine in a healthy genetic relative if he or she has inherited the familial *PRNP* mutation. Each individual has the option to discuss predictive testing with a genetic service.

Depending on the specific mutation, family members who inherit a mutation for prion disease are at varying risk of developing a genetic prion disease during their lifetime; however, some live to an old age without developing the illness and may die of other causes first.

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 (1–2 per million per head of population per year) and are classified as 'background risk'.

III.4 CONFIDENTIALITY OF PATIENT INFORMATION

Health care professionals have an ethical, professional and legal duty to protect patient information.[8] NPAAC has minimum standards for the retention of genetic test results for 100 years. The testing laboratory should report the *PRNP* test result to the requesting doctor only.

Genetic relatives can only request a copy of an existing *PRNP* test result from the testing laboratory through a specialist clinician or a genetic service.

Medico-legal and ethical implications of genetic information

Health insurance is "community rated", therefore a genetic test result has no implication for an existing policy but may impact the first year of a new policy. A person cannot be refused private health insurance on the basis of their present or future health status such as indicated by a genetic test result.[9]

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. A moratorium is in place allowing purchase of life insurance products up to a certain value without the requirement to disclose genetic test results (www.fsc.org.au/resources-category/standard/1779-standard-11-moratorium-on- genetic-tests-in-life-insurance/file)

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

III.5 INFECTION CONTROL FOR AT-RISK INDIVIDUALS

Infection prevention and control standard precautions apply for the care of a patient with suspected prion disease or a person at increased risk of developing prion disease. 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 risk status determined prior to the procedure.[10]

High risk patients:

1. Patients who report neurological symptoms and display neurological signs of prion disease or have been diagnosed with suspected prion disease.

2. Family members of a patient with suspected prion disease who fit into the following categories:

a. An individual has undergone predictive testing and has been confirmed as having a *PRNP* mutation.
b. An individual is from a family with a *PRNP* mutation 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 had CJD or another 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 family with a *PRNP* mutation and has undergone predictive testing and has a negative result for *PRNP* testing, then that person is classified as the same risk as others in the community (**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 meet 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:
www.health.gov.au/internet/main/publishing.nsf/content/icg-guidelines-index.htm

IV. PREDICTIVE TESTING

There is controversy around testing individuals under the age of 18 years for genetic conditions that have their onset in adulthood. The position statement from the Human Genetics Society of Australasia in relation to predictive testing for adult onset disorders can be found at www.hgsa.org.au/documents/item/1574 It is recommended that these guidelines be followed for predictive testing for *PRNP* mutations.[5]

Issues specific to *PRNP* predictive testing

PRNP predictive testing differs to 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 sporadic prion disease. Therefore, an individual who has inherited a *PRNP* pathogenic mutation or who has a relative who has a *PRNP* pathogenic mutation and has not been tested, should follow the infection control advice that is recommended for individuals with non-genetic prion disease and is outlined in point III.5 and the Australian National CJD Infection Control Guidelines.[10]

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

If a person has a deceased family member who was affected by a prion disease, but that family member did not have genetic testing, the individual can have testing of the *PRNP* gene. If a mutation is found, the individual 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 mutation.

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

V. CLINICAL GENETICS SERVICES:

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

Genetic counselling services in New Zealand:
www.geneticheathservice.org.nz/

VI. SHARING *PRNP* TEST RESULTS WITH THE NATIONAL CREUTZFELDT-JAKOB DISEASE REGISTRIES

The National Creutzfeldt-Jakob Disease Registries in Australia and New Zealand are under contract to the national Health Departments to perform nationwide surveillance and epidemiology of prion diseases and act as reference centres to ensure up-to-date surveillance practices and understanding of prion diseases in the healthcare setting.

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 prion disease in Australia and New Zealand. *PRNP* test results are analysed and reported for prion disease surveillance and epidemiology in a coded and de-identified manner. These data help advance the knowledge of prion disease, which may lead to a better understanding of risk factors and prevention of prion disease.

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

Appendix 1 – 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.385A>G (p.Met129Val) (Methionine/Valine) Codon 129 is homozygous c.385A>G (p.Met129VAL) (Valine/Valine)
219	Either glutamate (GAG) or lysine (AAG) Not reported

Appendix 2 – Consent form example

PRNP (DNA) testing options for patients with suspected CJD

Testing and/or storage options for future *PRNP* testing

Sample requirements:
At least 5 mls EDTA blood

Storage and/or testing options – please indicate below by ticking one option only:

Option 1

☐ DNA extraction and storage for future *PRNP* testing.
As genetic prion disease is rare most families wait for a 'brain only autopsy' confirmation of CJD before being referred to a genetic service to organise for *PRNP* testing on stored DNA from the CJD patient
(no cost)

Option 2

☐ *PRNP* testing (testing of DNA of suspected CJD patient) to establish or rule out a genetic cause.
NB: This test can be requested by a neurologist, geriatrician or genetic service but may incur a testing fee. PathWest will also require a referral document from the clinician's pathology provider to proceed with *PRNP* testing.

Signed consent form and blood sample to be sent to:

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

☐ I consent to the taking of a blood sample for storage and/or testing options as indicated above

☐ I also consent for *PRNP* results now or in the future to be provided to the Australian National CJD Registry (ANCJDR), for research and surveillance purposes in Australia, and to the Neuropathology team in my state if required to assist with diagnostic results.

Name of Next of Kin _____

Relationship to suspected CJD patient _____

Signed _____

Date _____

Name of requesting doctor _____

Facility_____

Signed _____

Date _____

For more information please refer to the 'Guidelines for *PRNP* genetic testing'
www.cjdsupport.org.au/resources/prnp-genetic-testing/

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 once autopsy confirmation of CJD is reported.

Diagnostic testing during the workup of a patient (Option 2) is recommended if there is a known family history or suspicion of a family history of prion disease.
A *PRNP* testing request can only be signed by a neurologist, geriatrician or geneticist.

Committee members and contact details –
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[2] Mastrianni J A: **The genetics of prion diseases.** *Genetics in Medicine* 2010, **12:** 187–195; doi:10.1097/GIM.0b013e3181cd7374

[3] **Minikel E V et al. Quantifying prion disease penetrance using large population control cohorts.** *Sci Transl Med*. 2016 Jan 20;8(322):322ra9. doi: 10.1126/scitranslmed.aad5169.

[4] Mead S: **Prion disease genetics.** *European Journal of Human Genetics*. 2006, 14(3):273-81. DOI: 10.1038/sj.ejhg.5201544

[5] Nance et al. ***Genetic testing for Huntington's disease: its relevance and implications***. 2001: hdsa.org/wp-content/uploads/2015/03/GeneticTesting-for-HD.pdf

[6] NHMRC – ***Medical Genetic Testing, information for health professionals.*** www.nhmrc.gov.au/guidelines-publications/e99

[7] ***Privacy Act 1988 (Cth)*** http://www6.austlii.edu.au/cgi- bin/viewdb/au/legis/cth/consol_act/pa1988108/

[8] ***Disability Discrimination Act 1992 (Cwth)*** www.legislation.gov.au/Series/C2004A04426

[9] ***Australian National CJD Infection Control Guidelines*** www.health.gov.au/internet/main/publishing.nsf/Content/icg-guidelines-index.htm

[10] **Literature** catalogue.nla.gov.au/Record/292457

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