

Institution: The University of Edinburgh
Unit of Assessment: 4
Title of case study: G: Diagnostic criteria for human prion disease enable case ascertainment and underpin international policy on prion disease
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Impact: Health and welfare; policy in the form of national and international guidelines; diagnostic service; engagement with patient groups.</p> <p>Significance: UoE-formulated diagnostic criteria adopted by the World Health Organisation (WHO), the European Centre for Disease Prevention and Control (ECDC) and US Centers for Disease Control and Prevention (CDC), enable reliable case ascertainment and longitudinal study of disease trends. The UoE Creutzfeldt-Jacob Disease Unit acts as an international reference centre for diagnosis. Case ascertainment has improved.</p> <p>Beneficiaries: Patients with prion disease and their families, policy-makers, the NHS, charities.</p> <p>Attribution: The UoE CJD Unit led the work with international collaborators.</p> <p>Reach: Worldwide; diagnostic criteria are WHO-endorsed and have been adopted worldwide. Pooling of data across Europe has enabled assessment of 11,000 cases of sporadic CJD.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>The UoE Creutzfeldt-Jacob Disease (CJD) Unit, led by UoE Professors Robert Will (Professor of Clinical Neurology, UoE, 2006–present), James Ironside (Professor of Clinical Neuropathology, UoE, 1994–present) and Richard Knight (Professor of Clinical Neurology, UoE 1996–present), has led the way in Europe with case ascertainment and diagnosis of human prion disease. The diagnostic criteria formulated and continually updated have been adopted by the World Health Organisation (WHO) and other international bodies for use worldwide. As a result, case ascertainment has improved and longitudinal trends in disease incidence can be mapped.</p> <p>The clinical diagnosis of human prion disease is potentially difficult, with a wide differential diagnosis. Currently, there are no validated, simple, non-invasive, disease-specific diagnostic tests. In addition, these diseases are, currently, untreatable, fatal and rare, with most clinicians therefore having limited experience. Effective diagnosis is important for patients and families, for the development of potential treatments and, given the potential human–human transmissibility of human prion diseases, has proven important for public health protection. Major policy decisions relating to the protection of the human population from bovine spongiform encephalopathy (BSE) in diet and from human–human secondary transmission of variant CJD (vCJD) infection via blood and blood products clearly depends on accurate case identification and resultant disease incidence and prevalence figures.</p> <p>The University of Edinburgh National Creutzfeldt-Jacob Disease Research and Surveillance Unit (NCJDRSU) has developed and validated diagnostic criteria for all forms of human prion disease, based on detailed study of suspect cases referred to it through the UK surveillance system it established in 1990, correlated with neuropathological diagnosis (2008–2012: mean 147 referrals/year; mean 102 pathological material cases/year). The formulation and validation of these criteria have been undertaken in conjunction with an extensive international collaborative network. Unit clinicians (Will, Ironside and Knight) and their scientific staff have visited suspect UK cases in life (mean 113 cases/year) and have visited families of cases identified after death, collected clinical and investigation results, and then have correlated these data with the final clinical and, whenever possible, the final pathological diagnoses [3.1–3.3]. They have then formulated diagnostic clinical and pathological criteria, and prospectively validated them on further suspect</p>

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case referrals [3.4, 3.5].

Recent relevant research (2009–) has involved the development of a highly specific cerebrospinal fluid (CSF) diagnostic test for sporadic CJD (the real-time quaking-induced conversion (RT-QuIC) test) [3.6], which is improving clinical diagnostic accuracy and is now in the first stages of consideration for inclusion in the clinical diagnostic criteria.

In 1993 Will established an international collaborative organisation that grew, with different groupings chaired by Will and Knight, to cover the whole EU plus other countries including China, Japan, Canada, Australia and Israel. The current organisation continues as the European CJD Surveillance Network (EUROCJD), chaired by Will. These international research and surveillance collaborations have received around €3M in funding.

Through the NCJDRSU's establishment and leadership of these international collaborations between 1993 and 2013, pooling of data from many countries worldwide has allowed the inclusion of large numbers of cases of these rare diseases (~11,270 cases of sporadic CJD). The Unit has also led, in collaboration with European partners, the use of supportive investigations such as cerebral magnetic resonance imaging and cerebrospinal fluid protein analysis (including the RT-QuIC test noted above), with harmonisation of methodologies and validation of application [3.2, 3.3, 3.5].

3. References to the research (indicative maximum of six references)

3.1 Chohan G, Pennington C, Mackenzie J,...Will R, Knight R, Green A. The role of cerebrospinal fluid 14-3-3 and other proteins in the diagnosis of sporadic Creutzfeldt-Jakob disease in the UK: a 10-year review. *J Neurol Neurosurg Psychiatry*. 2010; 81:1243–8. DOI: 10.1136/jnnp.2009.197962.

3.2 Meissner B, Kallenberg K, Sanchez-Juan P,...Will R, Zerr I. MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. *Neurology*. 2009;72:1994–2001. DOI: 10.1212/WNL.0b013e3181a96e5d.

3.3 Zerr I, Pocchiari M, Collins S,...Will R, Poser S. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology*. 2000;55:811–5. DOI: 10.1212/WNL.55.6.811.

3.4 Heath C, Cooper S, Murray K,...Ironsides J, Summers D, Knight R, Will R. Validation of diagnostic criteria for variant Creutzfeldt-Jakob disease. *Ann Neurol*. 2010;67:761–70. DOI: 10.1002/ana.21987.

3.5 Zerr I, Kallenberg K, Summers D,...Will R, Sanchez-Juan P. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain*. 2009;132: 2659–68. DOI: 10.1093/brain/awp191.

3.6 McGuire L, Peden A, Orru C,...Will R, Knight R, Green A. Real time quaking-induced conversion analysis of cerebrospinal fluid in sporadic Creutzfeldt-Jakob disease. *Ann Neurol*. 2012;72:278–85. DOI: 10.1002/ana.23589.

4. Details of the impact (indicative maximum 750 words)

Pathways to impact

The staff of the NCJDRSU disseminate their findings beyond academic publications and presentations. Real-time data on the worldwide incidence of variant CJD is freely available on the Unit's website [5.1], as is the trend incidence of vCJD, which is mathematically analysed by Public Health England. The Unit's website received 20,000 hits during 2012. The team presents an annual report to the UK Department of Health (DoH) and regularly provides data to the DoH in relation to parliamentary questions. In addition, senior staff make regular contributions to newspaper, radio and TV media.

Will, Ironsides, Knight and Dr Mark Head (Reader, UoE, 1998–present) regularly present to

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committees in the UK, Europe and USA, for example the World Health Organization (most recently in 2010), US Food and Drug Administration Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC; annually since 2009), the UK Spongiform Encephalopathy Advisory Committee (SEAC; 2009), the Advisory Committee on Dangerous Pathogens (regularly over the last 5 years), the Advisory Committee on the Safety of Blood, Tissues and Organs, the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (2008 and 2011).

Impact on public policy

NCJDRSU staff have played instrumental roles in advising national and international policy-makers. Will and Ironside have been members of the WHO International Health Roster of Experts since January 2009. The outcome has been that UoE data on the incidence of vCJD have profoundly influenced policy in the UK, and internationally [5.2, 5.3]: NCJDRSU diagnostic criteria [3.5] have been adopted by the WHO and ECDC [5.4]. The NCJDRSU is the sole external unit linked to the WHO vCJD web page [5.5] and, of the 22 citations underpinning the WHO guidelines on tissue infectivity, eight were generated by the Edinburgh group [5.6]. Informed by the European EUROCJD surveillance data, the case definitions for vCJD have been revised and now apply to all EU countries [5.7].

In the USA, Knight has been an invited expert companion on CJD Foundation/CJD Surveillance Centre annual visits to Congress/Senate to present data informing USA funding and policy (2009–2013). The 2010 US Centers for Disease Control and Prevention CJD diagnostic criteria were adapted from ref. [3.5] and the WHO criteria [5.8].

Impact on clinical practice

The case definition for vCJD in the EU is based upon the NCJDRSU diagnostic criteria and is applied via the ECDC. The Neuropathology Laboratory in NCJDRSU is an international referral centre for the diagnosis of all forms of human prion diseases, and the Unit acts as the hub for reporting of cases of vCJD to the EU (2010 onwards). It is the only infectious disease centre that remains outsourced from the ECDC [5.9].

The pattern of suspect sporadic CJD referrals in UK over the last five years suggests diagnosis by local neurological services has improved since reporting began in 1990; the number of identified cases has increased gradually over time, while the number of referrals remains approximately constant, although there has been variation. This probably reflects improved case ascertainment, particularly in those individuals over 70 years old, as discussed in the NCJDRSU Annual Reports 2009 and 2010. For example, identified definite and probable sporadic CJD deaths in the UK numbered 28 in 1990, 85 in 2010 and 90 in 2011. Furthermore, the annual mortality rate for UK sporadic CJD in the 75 to 79-years age group was 3.39 during 1990–1995 and 5.43 in 1996–2011 [5.1, 5.10].

The NCJDRSU's National cerebrospinal fluid (CSF) laboratory service has provided NHS clinicians and services with an important diagnostic aid, and the CSF protein test results, as defined by the Unit, are embodied in the current internationally agreed (and WHO-adopted) diagnostic criteria. The use of cerebral magnetic resonance imaging in diagnosis (adopted into the formal diagnostic criteria in Jan 2010) has been an additional significant aid to clinical practice and, through the Unit, Dr David Summers (NHS Neuroradiologist) has provided an expert opinion on scans in individual cases, both nationally and internationally. The newly developed and highly specific CSF RT-QuIC test has been audited by the Unit and has recently begun to impact on clinical diagnosis.

Impact on health and wellbeing

Effective diagnosis of CJD is important for patients and their families, and for clinical management. The NCJDRSU 's pooling of >11,000 cases across Europe is very important for meaningful study of the natural history of this rare disease and for the development of treatments.

Staff at the NCJDRSU are closely involved with CJD-related charities and patient support groups both in the UK and internationally. They make regular presentations to patient and family meetings

in the UK, USA, Italy and Australia, and have authored newsletters and information booklets for the UK charity, the CJD Support Network, which have been used as models for information provision in other countries. Will and Knight contributed to the clinical/diagnostic parts of the USA CJD Foundation educational DVD prepared for families and clinical professionals, and Knight was given the 2012 'Champion for CJD Families' award by the Australian CJD Support Network.

5. Sources to corroborate the impact (indicative maximum of 10 references)

- 5.1 NCJDRSU: Data & Reports [last updated Aug 2013]. <http://www.cjd.ed.ac.uk>. [Evidence for up-to-date incidence data.]
- 5.2 Advisory Committee on Dangerous Pathogens (ACDP) TSE Risk Assessment Subgroup Position Statement on occurrence of vCJD and prevalence of infection in the UK population London: Department of Health, UK, 2012. <http://media.dh.gov.uk/network/261/files/2012/08/ACDP-statement-vCJD-occurrence-and-prevalence-Jul-2012.pdf>.
- 5.3 Public Health England & Health Protection Scotland. Public health actions to be taken following a report of a new case of CJD or a person at increased risk of CJD. Colindale (London), 2013. http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1225960588712.
- 5.4 Official Journal of the European Union, Commission Decision of 28th April 2008. Available on request. [Adoption of the UoE criteria by the ECDC].
- 5.5 WHO manual for surveillance of human TSEs including variant CJD. WHO Dept of Communicable Disease Surveillance and Response 2003. Factsheet No. 180 (2012). <http://www.who.int/mediacentre/factsheets/fs180/en/>. [Link to the UoE NCJDRSU Unit on the WHO website.]
- 5.6 World Health Organization (WHO). WHO tables on tissue infectivity distribution in transmissible spongiform encephalopathies. Geneva: WHO, 2010, report no. WHO/EMP/QSM/2010.1. <http://www.who.int/bloodproducts/tablestissueinfectivity.pdf> [WHO guidelines on tissue infectivity; heavily influenced by UoE research.]
- 5.7 European Commission, 2008. 2008/426/EC: Commission Decision of 28 April 2008, Official Journal L 159, 18/06/2008 P. 0046 – 009. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:159:0046:01:EN:HTML> [European case definitions for CJD, informed by UoE surveillance data.]
- 5.8 US CDC Diagnostic Criteria for Creutzfeldt-Jakob Disease (CJD), 2010. http://www.cdc.gov/ncidod/dvrd/cjd/diagnostic_criteria.html [US CDC diagnostic criteria, formulated using UoE data.]
- 5.9 ECDC Framework Service Contract (2011). Available on request. [Evidence of the relationship between the NCJDRSU and the ECDC.]
- 5.10 European Medicines Agency: CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2011/06/WC500108071.pdf [Evidence of improved case ascertainment.]