Witness Name: Prof. Richard Knight
Statement No.: WITN5592013
Exhibits: WITN5592014-17
Dated: 18.04.2022

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF PROFESSOR RICHARD KNIGHT

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 15th October 2021

I, Professor Richard Knight, will say as follows: -

Section 1: Introduction

1. **Please set out your name, address, date of birth and professional qualifications.**

Address: GRO-C

Email: R.Knight GRO-C

Date of Birth: GRO-C 50

Current Employment: Emeritus Professor of Clinical Neurology,
National CJD Research and Surveillance Unit, Centre of Clinical Brain Sciences
University of Edinburgh

Qualifications:
BA (Oxon) [PPE]
BM BCh (Oxon) [Medicine]
FRCP(E)
BSc (OU) [Open: Maths & Physics]

2. **Please set out your employment history including the various roles and responsibilities that you have held throughout your career, as well as the dates.**

PRE-REG HS General and Vascular Surgery The Radcliffe Infirmary, Oxford
02.1977-08.1977

PRE-REG HP General Medicine Horton General Hospital, Banbury
08.1977-02.1978

SHO General Medicine/Geriatrics West Park Hospital, Macclesfield
02.1978-08.1979

SHO General Medicine/ Diabetes/Neurology Gloucestershire Royal Hospital
02.1979-02.1980

Registrar General Medicine/Gastroenterology Lister Hospital, Stevenage
02.1980-11.1980

Registrar Neurology Regional Department of Neurology, Derby
11.1980-02.1982

Research Registrar/Clinical lecturer Neurology/CJD Oxford
02.1982-10.1983

Registrar The Radcliffe Infirmary Oxford Neurology
10.1983-04.1986

Senior Registrar Neurology Northern General Hospital, Edinburgh
04.1986-09.1987

Consultant Neurologist/Hon Sen Lecturer Neurology Aberdeen RI

09.1987-12.1996

University of Edinburgh:

Honorary Senior Lecturer 1996-2004.

Honorary Reader 2004- April 2006

Reader May 2006-July 2008

Personal Chair Aug 2008-2017

Professorial Fellow 2017-2019

Emeritus Professor 2019-

NHS (Lothian University HT):

Consultant Neurologist 1996-April 2006

Honorary Consultant Neurologist May 2006-

NCJDSU/NCJDRSU Roles:

Clinical Neurologist	1996-2002
Deputy Director	2002-2005
Director	2005-2007
Deputy Director	2008-2009
Director	2009-2017
Clinical Neurologist	2017-
Epidemiology Lead	2021-

Provided Consultant NHS Neurology services at:

Aberdeen RI, Aberdeen

Raigmore Hospital, Inverness

Western Isles Hospital, Stornoway

Western General Hospital, Edinburgh

Dumfries & Galloway Royal Infirmary, Dumfries

Roodlands Hospital, Haddington

Newbattle GP Surgery, Newbattle,

Royal Infirmary of Edinburgh, Edinburgh

Comments:

1. 1982-83: Research post in the University of Oxford Department of Clinical Neurology, with Professor Bryan Matthews. Research in surveillance, clinical features and diagnosis of CJD in Egland and Wales.
2. From 1996 onwards, based in the NCJDSU (later called NCJDRSU), involved in surveillance and associated research, CJD, in the UK.
3. 1997 onwards Membership of International CJD surveillance/research collaborations.

3. Please set out your membership, past or present, of any committees, associations, parties, societies or groups relevant to the Inquiry's Terms of Reference, including the dates of your membership and the nature of your involvement.

a. Presently Continuing Roles:

i. Specialist Adviser to the vCJD Trust Committee 2002-
ii. Member of CJD Resource Centre Oversight Committee 2007-
iii. Chair of the UK CJD Support Network Management Committee 2011-
iv. Official Friend & Advisor to the CJD International Support Alliance 2009-

b. Past Roles:

i. Deputy Director & Director of NCJDRSU
ii. Member of the DH/MRC Research Advisory Group on TSEs
iii. Member of SEAC (Spongiform Encephalopathy Advisory Committee)
iv. Member of CSM Ad Hoc Expert Working Group on TSEs
v. Member of the Department of Health CJD Therapy Group
vi. Member of MRC Prion Disease Therapy Outcome Measures Group, CJD Therapy Group
vii. Member of MRC New Therapy Scrutiny Group
viii. Member of ACDP (Advisory Committee on Dangerous Pathogens)
ix. Member of ACDP TSE/Prion Sub-Group
x. Member of SaBTO Advisory Committee (safety of Blood, Tissues & Organs)

xi. Member (Observer) DH National Prion Monitoring Cohort Oversight Committee

xii. Member of STN Management Committee (Scottish TSE Network

xiii. Medical Advisor Member of the Human BSE Foundation Committee

xiv. Member of MSP (Organophosphates & Human Health) Veterinary Products Subcommittee

xv. Member of SCENHIR EC Committee on the Safety of Human-derived Products with regard to vCJD.

xvi. Chair, NEUROCJD (EU-funded CJD Collaborative Surveillance & Research in 10 European countries + Israel. (1998-2005)

xvii. Co-Chair EuroCJD (EU-funded CJD Collaborative Surveillance & Research in 10 European countries) (1998-2007)

4.The Inquiry understands you provided written and oral evidence to the House of Commons Science and Technology Committee. The written evidence to which you contributed is at TSTC0000039. Your oral evidence is at TSTC0000049. Please consider this evidence. Does it remain true and accurate? If there are matters contained in the oral evidence you gave that you do not consider to be true and accurate, please explain what they are.

a. I will confine my answer to those aspects for which I am directly responsible i.e. the written submission which was prepared as a consensus NCJDRSU document under my then Directorship and the (presumably faithful) recording of the evidence I submitted orally (but not the evidence others presented orally). My statements on these are:

   i. They were, according to all I knew then, indeed accurate and true at the time of submission.

   ii. There have been some developments since then that are additions to the evidence but they occurred since the time of those submissions. As these developments are dealt with elsewhere, I will not go into detail here but simply list the important ones:

      1. The Appendix III Study has been completed and published (RLIT0000725).

2. Further work relating to the Appendix samples is progressing [no results yet available].
3. There has been a definite MV vCJD case identified (WITN7034010).
4. There have been publications concerning blood tests for vCJD but the points made about the necessity for proper evaluation and the difficulties of this still stand (NHBT0033626, WITN5592003, WITN5592004).
5. The prepublication papers concerning vCJD and Blood mentioned in Q 191 have been published (WITN5592005).
6. The study of the elderly mentioned in Q179 was agreed, funded and started, essentially as a feasibility study as there were considerable methodological concerns about the ability to undertake a study of elderly dementia cases even within a single locality such as the Lothian region. This study is completed and a paper is in pre-submission form. No unsuspected cases of vCJD were found.

5. Please confirm whether you have provided evidence or have been involved in any other inquiries, investigations, criminal or civil litigation in relation to the human immunodeficiency virus ("HIV") and/or hepatitis B virus ("HBV") and/or hepatitis C virus ("HCV") infections and/or variant Creutzfeldt-Jakob disease ("vCJD") in blood and/or blood products. Please provide details of your involvement.

I have been involved in WHO Consultations on CJD.

I have presented evidence to the FDA on CJD.

I have provided expert opinion legal reports in two cases:

i. In relation to the possible exposure of an individual to the risk of vCJD related to albumin
ii. In relation to the possible exposure of an individual to the risk of vCJD from a hospital error in the use of plasma.

I provided a report and attended Court as an expert witness in relation to a vCJD family requesting a Health Authority to give their son, who had vCJD, an unproven treatment (intra-cerebro-ventricular Pentosan Polysulphate).

Section 2: Knowledge of Risk of vCJD transmission via blood transfusions and blood products.

6. A chronological summary list of journal articles that you contributed to which relates to addressing the emergence, discovery and scientific development over time of the risks of vCJD infection and the risk of secondary transmission via blood and blood products.

I have listed all my publications relating to prion disease at Appendix 1.

7.Please summarise the steps which the committees and organisations you were a part of took, if any, to ensure that the government and NHS bodies were informed about the risks of vCJD transmission via blood and blood products.

a. The NCJDSU/NCJDRSU made our surveillance and research findings available to others, in a timely manner, via:

i. Publications
ii. Presentations to meetings of professional bodies (such as the Association of British Neurologists, blood transfusion society meetings etc)
iii. Presentations at national and international research meetings
iv. Our Annual Reports
v. Our Website
vi. The NCJDSU/NCJDRSU made our data and findings available to the Department of Health both on a routine basis and via particular communications when there were fresh developments of relevance to public health and policy. The DH was provided with pre-publication

copies of pending publications. Our data relating to blood and vCJD were provided to blood services in a timely fashion.

vii. The NCJDSU/NCJDRSU provided data for answers to be given by officials to Parliamentary Questions on CJD/vCJD topics.

viii. The NCJDSU/NCJDRSU made our data and findings known to expert committees (such as ACDP, SEAC, SaBTO etc) either via Unit staff being members of the committees or by regular reports to these committees as requested by these committees.

8. An account of your understanding of the relative risks of vCJD infection from the use of domestically sourced blood and blood products and the use of commercially supplied blood products.

The question relates to my understanding of the *relative* risks of vCJD infection: From (a) domestically-sourced blood and (b) From domestically-sourced blood products relative to commercially-supplied blood products.

a. My understanding is that domestically-sourced blood would not be donated by individuals with clinical vCJD, who would, if normal practice were being followed, be deferred as donors, being obviously unwell. The risk would come from donors with (unidentifiable) asymptomatic vCJD infection. The magnitude of this risk is very uncertain as all of the relevant factors are uncertain:

i. The prevalence of asymptomatic infection in the UK population

ii. The significance of any distinction between pre-clinical and subclinical infection.

iii. The amount of infectivity in the donor's blood (and, therefore, any donation).

iv. Whether this level of infectivity changes over time.

v. The distribution of any infectivity in blood different components.

vi. All of the factors that govern susceptibility to infection of the recipient.

b. This question refers to 'blood' which might, in this context, refer to various labile blood components. However, in my response, I will deal

with RBCs (Red Blood Cells) since the general comments I will make could be extended to other labile components. In general, my understanding is that it is not possible/realistic to import things like RBC Units from elsewhere. As far as I am aware, most countries are just self-sufficient in terms of RBC Unit donations/use, with no realistic opportunities for exporting RBC Units in the number required for UK use (each year, the UK transfuses approximately 2.5 million Units). In addition, RBC Units have a limited shelf-life (around a month). Each country essentially has to rely on domestic supply, with only occasional imports of, for example, Units of rare blood types. Therefore, in terms of the question, the *relative* risk must refer to the risk of using a domestic product compared with not using any product at all. There are situations where the risk of not using RBCs is death or serious medical harm and these events occurring over the immediate future such as measured in minutes or hours (for example, serious trauma involving haemorrhage). In such situations, the relative consideration is of a possible infection possibly resulting in illness in 10 or more years time, compared to certain or probable relatively immediate death/serious harm. There are other situations, such as ones involving elective surgery where a small volume of blood might or might not be required. In these situations, autologous donation can be considered to avoid any risk from other blood and this is, according to my understanding, practised where appropriate. Finally, there are situations where other treatments might be considered to avoid the use of donated blood. For example, maternal blood loss during parturition might be treated with a course of oral iron. Therefore, if medical practice follows rational principles, the use of RBCs is essentially unavoidable in most, if not all situations where they are in fact used.

c. In contrast, blood products can be imported and so the *relative* risk is a matter of comparing the risk from using domestic products compared to imported ones (the question uses the term 'commercially supplied blood products'; there could be domestically commercially supplied blood products but the question would then be meaningless, so I am interpreting the question in terms of domestic vs imported). If products

were produced from foreign blood donations, particularly donations in non-BSE/non-vCJD countries, then these products certainly would be safer from a potential vCJD risk point of view, than those of UK origin (to assess the actual relative safety one would need to know the actual UK risk and the degree of certainty of BSE/vCJD freedom in the other country). On the other hand, it might be that products from another country might be more risky, or less efficacious, for conditions other than vCJD. I do not feel able to comment on other potential risks, but understood they were considered by other (blood) experts in deciding on policies to import plasma products.

Section 3: Actions and Decisions

9. **Please provide an outline of any proposals, whether accepted or not, that were made by any relevant organisation you were a part of, whether during your tenure or otherwise, in an effort to protect the blood supply from the risk of vCJD.**

This is a very difficult question to answer in full and reliable detail and I can provide information only to the limit of my memory. My personal involvement was as part of the NCJDRSU and as a member of relevant advisory committees. As such, I provided observational data (such as numbers of cases, details of blood-transmission events that were identified etc), took part in discussions around possible interpretations or significance of such data, but had no direct role in policy decision.

a. Screening or Diagnostic Tests

Diagnostic tests were discussed on many occasions in many fora. Developments and assessments of diagnostic tests were discussed regularly in informal settings, research meetings, collaborative surveillance meetings, and in different advisory committees. I give details of relevant considerations in paragraph 12 below.

Screening tests are, essentially, a special subset of diagnostic tests

but with the important characteristics that (i) they need to detect abnormality in tissues such as blood from individuals who are asymptomatically infected and (ii) they need to be usable on a bigger scale, in a timely way, than just what might be required for diagnosing illness in a single ill person. In other words, a test to diagnose a single ill person that takes several days to give a result, requires a special laboratory technique, and costs, say, £200, might well be feasible for use in this clinical diagnostic situation, but might be impossible to scale up in a practical way to screen hundreds of blood donations with a result required within hours. In addition, any test has positive and negative error rates which might give rise to quite different difficulties when the test is applied to many samples from a population with a low risk of infection, when compared to its use in one person who is ill with what is already suspected to be that infection. The possibility of screening blood donations using the blood test described by Edgeworth et al (see discussion in Paragraph 12 below) (NHBT0033626) was certainly discussed in various fora, at various times. On those occasions, the decision against such a use centered on: (i) it was not known if the test detected asymptomatic BSE/vCJD infection, and, if it did, with what degree of sensitivity or specificity , (ii) how such uncertainties could actually be resolved and (ii) The test, as it stood then, could not be scaled up simply to use appropriately and practically in NHS donation situations. I do not know of any discussion of whether any other tests could be used for screening purposes.

b. Filtration Policy

The possibility of using vCJD-effective blood filters was discussed in various fora at various times. The fundamental concerns were: (i) the effectiveness of filters on vCJD, (ii) the possible deleterious effects that filtration might have on products and the practicalities of introducing wide-scale filtration. One problem was how the effectiveness of filtration in removing vCJD infection could be reliably determined. Results from animal models or blood 'spiked' with infective material might not be directly transferrable to 'natural'

infectivity in blood donations and it was impossible to supply blood from vCJD patients in the amounts required in order to undertake the experiments that would be needed. There was also the difficulty of how to reliably assess infectivity in blood.

c. **Quarantine of batches** I am not able to add further detail on this specific topic.

d. **Donor Selection & Exclusion Policies** Any selection/exclusion policy must be considered in terms of:

   - The degree of risk reduction it would lead to.
   - Its cost/ease of implementation.
   - Its potential effect on those who wish to donate blood.
   - Its potential for reducing blood supply.

   As discussed above (in paragraph 9a), there was no practical donor/donation screening test and the general population was considered to be at some potential risk of being infected with vCJD. One exclusion policy was the exclusion from donation of those who had received a blood transfusion. My understanding was that such a policy could help to prevent potential 'recycling' of any vCJD blood-related infection, was easy to administer and would not have serious effects on overall blood supply. I believe that there were considerations that such a policy might have other non-vCJD benefits, but this is an area outside my specific expertise. I am not able to add further detail on this specific topic.

e. **Product Recall** I am not able to add further detail on this specific topic.

f. **Recombinant blood products** I presume this relates to matters such as recombinant Factor VIII. I am not able to add further detail on this specific topic.

g. **Importation of product from the USA/elsewhere** I am not able to add further detail on this specific topic.

h. **Surveillance** I am not sure as to what is being asked here.

The question relates to proposals about surveillance. The details of UK CJD national surveillance (see WITN5592001), the TMER and other studies are discussed at section 5 in this statement and I have no further detail to provide.

10. When and by whom any proposals were made.

a. The various discussions were conducted over time in various contexts, giving specific individual detail as exactly when they took place and with whom would be extremely difficult and almost certainly inaccurate. The same is true to some degree in relation to specific proposals. However, as far as proposals are concerned, any that were made, discussed, adopted or not, in committee settings would be recorded in minutes of those committees (such as SEAC, ACDP, SaBTO and any relevant DH or Blood Services Committees). I am able to comment in more detail on Surveillance, if that refers to the TMER study. Details relating to the TMER study are discussed at section 5 in this statement.

b. The factors considered when deciding whether to implement these proposals.

The various factors which would enter into any such discussions could be divided into two main groups: Risk Analysis (i.e. the assessment of the risk of vCJD blood-related transmission) and Risk Management (i.e. the practicalities, acceptability, costs and opportunity costs of any proposals put forward to try to reduce vCJD risk). Indeed, in all such discussions that I myself witnessed or took part in, both these aspects were always considered. One problem with the risk analysis aspect was (and is) a great deal of uncertainty about most of the relevant facts (such as how many donors might be silently infected, the level of infectivity in blood from infected donors etc). The risk management process had to take into account many factors such as: could a proposal actually work at a national blood service level? Would the

cost of any proposal make blood transfusion unaffordable? Would any proposal lead to blood donor and/or blood shortages? What would be the adverse health impact of proposals (including possible deaths due to blood restrictions)?

Details relating to the TMER study are given at section 5 in this statement.

c. Decisions made on such proposals, including the date on which they were made or rejected.

Since December 1997, all blood components, blood products or tissues obtained from any individual who later developed clinical vCJD were withdrawn and recalled to prevent their use.

i. Since 1998, synthetic (recombinant) clotting factor for the treatment of haemophilia has been provided to those under 16 years of age and, since 2005, this measure has been extended to all patients for whom it is clinically appropriate.

ii. Since October 1999, white blood cells (which are thought to contain most of the infectious agent that causes vCJD) have been reduced in all blood components used for transfusion, by leuco-reduction.

iii. Since 1999, plasma for the manufacture of fractionated plasma products, such as clotting factors and immunoglobulins, has been obtained from sources outside the UK.

iv. As of 2004, all individuals who have received a transfusion of blood components (anywhere in the world) since January 1980 have been excluded from donating blood.

v. Since 2004, plasma for transfusion to those born on or after 1 January 1996 has been obtained from outside the UK.

vi. Since 2005, platelets have been collected from a single donor by apheresis for transfusion to children under 16; in 2013, this was extended to include all individuals born on or after 1 January 1996.

vii. From 2009 to 2013, a minimum of 80% of platelets were collected from single donors by apheresis, for transfusion to all recipients. This measure was reassessed and rescinded in 2013.

The Safety of Blood, Tissues and Organs committee (SaBTO) recommended that the provision of imported plasma and apheresis platelets for individuals born on or after 1 January 1996 or with thrombotic thrombocytopenic purpura should be withdrawn, but that other risk-reduction measures for vCJD should remain in place.

In 2020, the UK lifted its ban on the use of UK plasma to manufacture plasma-derived immunoglobulin products that was introduced in 1999 to mitigate the risk of vCJD transmission.

In relation to the reference in the question to proposals that were rejected and the dates on which they were rejected, I am not able to give accurate, detailed, information. Possibilities were discussed in various fora, at various times, that did not lead to specific positive actions, but I am not sure whether any or all of these were specific proposals that were formally 'rejected'. For example, plasma filtration and donor screening were discussed but neither were implemented. I am not able to recall specific dates, nor all of the contexts in which discussions took place. The minutes of committees such as SaBTO will record any occasions of such discussions. The reasons-as I understand them-that such possibilities did not lead to positive action are discussed elsewhere in this statement (see Paragraphs 9a and 9b).

d. How any such measures were implemented in practice, including efforts made to monitor their effectiveness.

I am not able to detail exactly how the above measures were implemented in practice and the question would have to be addressed to those bodies that undertook the practical implementation. As to how they were monitored for effectiveness, there are two broad answers. Firstly, the actual monitoring of

the measures is a matter for those bodies, such as the Blood Transfusion Services, who implemented and undertook them. Secondly, CJD national surveillance, the TMER study and other studies (such as the Primary Immunodeficiency Study ("PID"), the Haemophilia study, etc) continued surveillance of CJD cases and possible blood connections. This surveillance, and associated studies, is obviously an indirect assessment of protective precautions, in that it identifies if transmissions are taking place, or not, and, if they are, at what level, and by what means.

11a. Your opinion as to whether the risk of secondary transmission via blood and blood products was adequately mitigated in the UK in line with what was known about the potential risks of vCJD at that time.

My personal opinion is that the consideration of the risk of vCJD from blood and blood products in the UK was appropriate in detail, care, and timeliness. Detailed discussions of risk took place in the immediate wake of the identification of vCJD, before any instance of transmission of human prion disease by blood had been identified, and despite previous expert opinion that blood transmission was unlikely. Actions were taken in a precautionary manner, balancing potential vCJD risk against any risks of any actions taken. To be clear, all precautionary actions related to reducing potential vCJD blood risk could have potentially harmful effects of their own.

11b. Your view as to whether any decisions or actions could and/or should have been made earlier and how this might have impacted the number of individuals considered to be at risk of developing vCJD.

i. My personal view is no earlier actions, or other actions, should have been taken, given all that was known at the time. The 3 cases of clinical vCJD (and the single case of asymptomatic vCJD infection resulting from blood) related to RBC transfusions that were donations from individuals not known to have vCJD infection at the time of donation and the time of use of those donations (NCRU0000109_082). RBC transfusions are necessary in certain clinical situations and the only realistic source of RBCs is domestic.

They were not leuco-reduced donations and it is impossible to say whether transmission would have not occurred if they had been leuco-reduced; the level of infectivity in pre-clinical vCJD blood remains uncertain as does the magnitude of the effect of leuco-reduction (although experimental evidence indicates that it does not remove all infectivity) (WITN5592014). There is a single possible case of asymptomatic infection related to a blood product (Factor VIII) (HCDO0000799).

ii. The fact that no further cases of blood or blood product related vCJD have been identified can be explained on only 3 grounds:

1. The precautionary measures taken were very effective.
2. The risks were, in fact, not as great as the precautionary estimates assumed.
3. Cases of vCJD transmission have occurred but not been identified.

iii. The explanation may be one of these, a combination of two of them or a combination of all three. It is impossible to comment definitively on which of these possibilities hold, however, while it is difficult, or arguably impossible, for any disease surveillance system to consistently identify all cases, from my experience, I do not think it credible that missed instances of blood-related infection is any more than a possible, minor, factor. There have been analyses of UK surveillance data to ascertain if some blood-transmission cases might have been missed, with no evidence to support that there is a significant number of unrecognised cases (WITN5592015). The precautionary measures would obviously have effects but RBC transfusions have continued without further cases and my personal view is that the risks are, in fact, significantly less than were first assumed. This is not necessarily surprising as those assumptions were made in the face of great uncertainty about some facts and actions were taken according to the precautionary principle, with modelling including some worst-case assumptions. Important actions were indeed taken on a precautionary basis, before actual evidence

of risk, and within a short time period from the identification of vCJD as a disease (1996). Blood components and products from vCJD individuals were withdrawn from use in 1997. Universal leuco-reduction was instituted in 1999. Plasma for fractionated blood products was sourced outside the UK from 1999. Some actions (such as universal leuco-reduction) take time to institute for irreducible practical reasons.

12a. What test did the Prion Clinic want to use?

The question refers to document NCRU0000109_014. This document is the minutes of a meeting I did not attend. From the text and the date, I presume the test is the blood test for vCJD that was described in a publication by Edgeworth et al in 2011 (NHBT0033626).

12b. What was your view of the test? What did you say to the Department of Health about the test? Has your perspective on this since changed? If so, why?

i. In the minutes (NCRU0000109_014) it is stated that I simply let the DH know of plans to use this test as a diagnostic test on patients with suspect vCJD. After over 10 years, I cannot recall what I said to DH, exactly when or by what means. However, the NCJDRSU had regular contact and discussions with the DH. As far as I can recall, my view of the test at that time was that it was an interesting development and one that could prove very useful. However, the data available then were limited and any test needs to be validated carefully before it can be adopted into routine diagnostic practice. For example, the CSF RT-QuIC test for sCJD was evaluated in a large number of samples and then evaluated in surveillance for some time before being adopted as a routine test and included an internationally agreed diagnostic criteria. One needs to establish the sensitivity and specificity of a test and its positive and negative predictive values. Of course, this was, and remains, a difficult matter for proposed vCJD tests since there were (and still are) a very small number of blood samples from past

cases and very few (currently none) new cases to test. My view then was that that particular test needed more assessment before it could be used as a routine diagnostic test-to avoid problems that might arise from false positive or false negative results. All the tests that have been/are used in the routine diagnosis of CJD, including vCJD, such as CSF 14-3-3, CSF Rt-QuIC and MR imaging appearances, have been subject to careful validation before use; my opinion was that any blood test should be equally carefully validated. There were other considerations at that time such as the type of blood sample required by the test and the fact that it required a particular anticoagulant to be used in the sample collection.

ii. My perspective on the validation of tests has not changed.

iii. To the best of my knowledge, the test in question has been studied further but is still not validated adequately for routine diagnostic use. As far as I am aware, it has given positive results in samples from 1 or 2 sporadic CJD cases and so is not totally specific for vCJD. Other blood tests have been developed since but, again, not adequately validated for routine diagnostic use.

iv. The discussion above relates to the use of this test as *a clinical diagnostic tests in individuals who are ill and suspected as having vCJD* and to other possible use (since the discussion noted in the minutes to which the question refers relate to this particular use).

12c. Have any effective diagnostic pre-symptomatic blood tests been developed since?

Yes, although it has not been possible to validate any test adequately. The only test that has definitely given positive results in pre-symptomatic blood from vCJD cases is that described by Bougard D et al, 2016 (WITN5592004). The evidence relates to samples taken during routine blood donation, from two individuals who later developed vCJD. There were only 2 such individuals with such samples. These individuals donated in France and were French vCJD cases.

This test has been evaluated in clinically ill vCJD cases and in 2 pre-clinical instances (identified as such by their later illness and diagnosis) but it is not possible to comment on its utility in subclinical vCJD.

12d. Practical Issues arising out of ownership/custodianship of vCJD samples by different institutions and how this affects the research and development of such diagnostic tests.

i. Samples from patients suspected of having CJD (including vCJD), including those who turn out to have vCJD, are collected by the NCJDSU/NCJDRSU according to the ethically approved arrangements of the Unit's surveillance and research protocols. Consent is obtained to take the samples, hold them and to use them for defined purposes. These samples have included CSF (cerebrospinal fluid), blood and urine. Other tissues from autopsies and biopsies (such as brain and lymphoreticular tissue) are also held. The practical issues arising from this ownership/custodianship of vCJD samples are simply those of appropriate, safe storage. The other issues are those of responsible use, in line with the consent for holding them.

ii. The NPC/MRC Prion Unit also hold samples, including blood from vCJD individuals.

iii. The particular importance of the vCJD blood specimens is their rarity. With approximately 60 cases of sCJD each year in the UK, there are many opportunities for obtaining blood samples for sCJD. In the UK, there have been a total of 178 cases of Definite/Probable vCJD to date, with, therefore, a limitation on available samples. The samples were collected in line with the surveillance/research aims of the NCJDRSU and NPC: *PRNP* mutation testing, codon 129 determination and specific research projects. Initially, there was no call on these samples other than from the two units that held them but other researchers became interested in access to them especially as

other groups started to develop possible blood tests that they wanted to validate. There was concern in both Units as to how decisions about access to these scarce samples might be governed fairly and appropriately. In 2007, a committee, independent of, but with representation from, both units, was set up to review proposed use of samples by groups outside the NCJDRSU and NPC.

iv. The background to this is described in The House of Commons Science and Technology Committee Report, "After the Storm?" and I will not repeat all the detail here (TSTC0000052). The committee underwent a few changes in name, is still constituted under the name of the 'CJD Resource Centre Oversight Committee'. I am a member of this committee but it has not met since 2019. The CJD Resource Centre is based within NIBSC (the National Institute of Biological Standards and Controls) which is a body of the MHRA (Medicines and Healthcare Products Regulatory Agency). The Resource Centre held, and holds, a variety of tissue samples related to human and animal prion diseases. The aim of the Centre and the Oversight Committee is to establish whether candidate test methods are able to identify blinded plasma or other blood samples from infected individuals with acceptable specificity, sensitivity and reliability.

v. The committee decided on a plan of access to samples which required a blood test developer to progress through a series of requirements, beginning with satisfying the committee about their initial research, progressing through the successful evaluation of 'spiked' plasma ('spiked' with tissues of known infectivity eg spleen and brain from vCJD cases), specimens from infected experimental animals and, eventually, onto the scarce human vCJD samples. These various samples were prepared as standard panels, provided 'blinded' and with control samples. The committee evaluates the results from each stage before deciding on whether progression to the next stage should occur. The aim being to ensure that only tests with a reasonable chance of success should be used on the scarcest specimens.

vi. The protocol was described in a publication in 2013 by Cooper et al (WITN5592016).

vii. Both units, the NCJDRSU and the NPC, provided some of their vCJD samples to the Centre, although retained samples for their own research studies.

viii. In relation to the specific supplementary question: "Is there any research to date which has investigated synthetic/recombinant vCJD samples?", from its wording/terminology, I do not fully understand what is being asked. However, I do not know of any research on diagnostic tests that is based on methods other than concentration/detection/amplification/experimental transmission of vCJD using material from animals or humans.

Section 4. Notification exercises

13. Please summarise the steps which the committees and organisations you were a part of took, if any, to ensure that the medical profession and implicated patients were informed about the risks of vCJD transmission via blood and blood products.

The NCJDSU/NCJDRSU did not, and do not, notify individuals of any 'at risk' status. This is a matter for the Blood Services/Public Health bodies. The NCJDSU/NCJDRSU is not a member of any organisation that takes such actions.

The NCJDSU/NCJDRSU provides data to organisations such as DH and members of the NCJDSU/NCJDRSU have been members of advisory committees that provide data and advice to organisations that deal with notification of 'at risk' status.

It is difficult to know what level of detail to be given here. The basic point is that the NCJDSU/NCJDRSU provided prompt, up-to-date information, from UK surveillance and projects like the TMER, to committees, Blood Services, DH and medical professionals in order to inform discussions and decisions.

14a. Summary of issues surrounding notification of risk to individuals deemed to be at risk of vCJD.

i. Of course, the discussion here relates to those at *increased* risk of vCJD, relative to the general UK population (all of which are deemed to be at some risk of vCJD through dietary exposure).

ii. A proposal to identify recipients of blood that had been donated by individuals who, while being healthy at the time of donation, later developed vCJD, does raise ethical questions, especially in the contemporary absence of evidence of blood transmission of vCJD. Firstly, identification of the recipient would mean holding information that they had been exposed to a theoretical risk of a serious infection. Holding that information about them, without informing them, is an ethical concern. On the other hand, informing them leads to other ethical concerns including potential psychological damage from such information, especially given the uncertainties of the risk and the fact that no confirmatory test of infection or treatment is available.

iii. As another consideration, if individuals who had received a vCJD-implicated blood transfusion were to turn up at a donor centre to give blood, what should be the action? If the donation was accepted, could this be seen as exposing others to a theoretical risk? If the individual were to be rejected as a donor, then would they be told why? If so, they would then be informed of the exposure of which they may previously have been unaware. If they were allowed to donate, but the donation then secretly discarded, this poses clear ethical concerns. If this situation were to be avoided by telling recipients of the theoretical risk, it could be a very mixed message: 'you may have been exposed to a risk but its only theoretical and no transmission has ever been identified, so don't worry but, by the way, you are not allowed to donate blood as it might be a risk to others.' There is a clear potential for psychological damage to those informed, especially when there is no known method of testing for whether the person is infected, nothing they can do to prevent disease and with the risk being present for years or even decades. On top of this, at certain stages of the consideration, there was no actual evidence that blood did transmit disease and the magnitude of this risk remains uncertain. These concerns then have to be considered in the light of the potential public health considerations of possible risk to others.

14b A summary of the views, opinions & decisions regarding notification arising from the CJDIP consultation process in 2000.

The CJDIP (CJD Incidents Panel) was set up in 2000. I was not a member of the CJDIP. I am not sure what is meant by the 'CJDIP consultation process'. I am not able to provide an answer to this question.

15a The policies and practices implemented in the UK with respect to notification and de-notification.

The NCJDRSU was not responsible for notification/de-notification nor policy-making. This responsibility lay with the National Blood Services and bodies such as the Health Protection Agency/Public Health England and, local public health teams. My understanding is that the CJDIP assessed the possible risks resulting from potential exposure and advised on the 'at risk' status but did not directly notify or de-notify individuals. There are details in The House of Commons Science and Technology Committee Report, "After the Storm?" (TSTC0000052).

15b An account of what, how, when and where notifications of risk were told to those with potential exposure to vCJD infection.

i. When: As far as I am aware, people were notified as soon as practically possible after a defined exposure to risk was identified.

ii. How: As far as I am aware, the notification was made, in the first instance to the relevant General Practitioner or other local clinician and the decisions relating to notification of the individual left with them. This allowing factors such as the mental or physical condition of the individual to be taken into account and for there to be an individual who could provide continuing local support. I presume that the usual method was face-to-face, but I do not know the details of every notification.

iii. What: There were information leaflets available (as detailed in The House of Commons Science and Technology Committee Report, "After the Storm?" (TSTC0000052).

iv. Where: Presumably some local venue such as their home, the GP surgery or local hospital.

v. Leaving notification to local doctors-such as GPs-had one clear drawback in that such medical professionals would not have detailed knowledge or understanding of all aspects of prion disease.

vi. In relation to what people were told, it was anticipated that some notified individuals would be particularly anxious, and/or require more detailed information than their local doctor could provide, and/or require additional support. Such individuals had the options of contacting the NCDRSU, the NPC or the CJD Support Network (CJDSN). Certainly, I recall some individuals contacting the NCJDRSU for further discussion and individuals contacted the charity, the CJDSN, as well.

vii. As an example of the possible NCJDRSU involvement: In 2018, I visited someone (who had been told she was at risk from a blood transfusion) at their home. She had become concerned that they had symptoms suggestive of vCJD and had consulted her GP. I went to see her, went over her symptoms and examined her. I wrote a detailed letter to her GP saying that there was no evidence of vCJD at that time. As far as I am aware, she died a couple of years later from non-CJD causes.

15c My view as to whether patients should be notified.

i. The Inquiry refer to a letter I wrote on this subject in January 2000 [NHBT0004320]. This letter discusses many issues surrounding notification and I do not think I have a lot to add to what was said in that letter. Two things have changed since that letter was written: (i) blood transmission has been identified and (ii) further blood tests have been developed and one of these proved able to detect pre-clinical

vCJD in blood samples from 2 individuals. However, as discussed at paragraph 12.c, these tests have not been properly validated as asymptomatic infection tests and I would refer to the comments I made in the letter about tests in general. Leaving aside the difficulties of uncertainty about the actual magnitude of any risk, two core problems in notification are:

1. The right of the individual to know that they are 'at risk' has to be balanced against the right of the individual not to know (at least in my view). Especially as there is no action they can take to determine if they are infected, to determine if they will become ill or to take action to prevent it.

2. The public health protection measures that may be deemed necessary to stop any infected person infecting others.

ii. There is an obvious conflict between the right not to know and the need to protect others. If we are taking measure to protect others, these measures can be divided into two groups. Firstly, they could be justified on general grounds that do not necessarily relate to vCJD and so do not necessitate informing an individual of specific vCJD risk. For example, all blood recipients cannot donate blood in order to reduce the risk of maintaining any infection in the blood supply. Secondly, they are individual and necessitate informing the individual of a specific risk. For example, 'you must take certain precautions with some medical interventions and procedures because you are at risk of vCJD'. For this second, group, certain developments could overcome the need for specific notification. For example, if a practical means of universal sterilisation that inactivates vCJD infection were available, then perhaps all instruments could be processed this way and then no specific measures would be needed in this respect for individuals who are deemed 'at risk'. Again, one should add that being 'at risk' from blood is actually being at increased risk, since the population in general (alive in the UK between 1980 and 1996) is deemed to be at risk of vCJD infection and/or illness.

iii. As far as any discussions I have had (either through the NCJDRSU

or the CJDSN) with individuals notified as being 'at risk', the content of the discussion has been tailored to meet the individual circumstances and concerns. However, in general, I have tried to indicate that the risk is low; with the passage of time and the accumulation of data, I have felt able to be more reassuring on this. I have also indicated to them that the public health actions (such as being deferred as donors or regulations around medical instruments) are taken as precautions and do not, in themselves, indicate that the individual is actually infected nor that the risk of being infected is high.

16. The Inquiry is aware that three confirmed cases of vCJD infection via blood transfusion occurred. Did these three cases occur before or after the implementation of leucodepletion?

a. As it stands, it is not the case that 'three confirmed cases of vCJD infection via blood transfusion occurred'. From blood (Red Blood Cell) transfusion, there have been 4 cases of vCJD infection; in 3 cases vCJD disease resulted and in 1 case, there was evidence of asymptomatic/subclinical infection (NCRU0000109_082).

In all 4 instances referred to above, they received non-leuco-reduced blood; the transfusions took place prior to the introduction of universal leuco-reduction.

b. Elsewhere it has been reported that these three cases of vCJD were caused through administering the blood of an asymptomatic infected donor. Please confirm if this is correct or not, and if correct, set out how it is known that the donor was asymptomatic.

All 4 cases resulted from blood donated by individuals who later developed vCJD. At the time of donation, they were well and, in particular, had no symptoms of vCJD. Following dietary exposure to, and infection with, BSE, there is a long silent, pre-symptomatic, period (the 'incubation period') during which the affected individual is entirely well and their vCJD-infected status is unknown. If they had been ill at

the time of attending to donate, they would have been deferred by the Blood Donation Centre. In addition, the NCJDSU/NCJDRSU knows they were asymptomatic at the time of donation as we have detailed information obtained through our surveillance practice that allows us to ascertain the date of onset of their vCJD symptoms.

17. In 2014 you gave oral evidence to the House of Commons Science and Technology Committee. At that committee meeting, Stephen Mosley asked whether "an individual who died from vCJD infection might have contracted it via blood transfusion after the introduction of blood safety measures in 2002" (TSTC0000049, page 18). In your response, you noted that you were not aware of any such case. Have you since become aware of any such case? I have not become aware of any case of vCJD infection resulting from donated blood after the introduction of the blood safety measures in 2002.

18. (a) "How effective is leuco-depletion at reducing the subclinical risk of vCJD in blood donations?".

I am not entirely sure as to the meaning of 'subclinical risk' as it is phrased here. However, if the question is asking about the effectiveness of leuco-reduction in reducing any vCJD infectivity in donated blood, there is no definite answer. Certainly, it is not possible to state its effectiveness in reducing infection risk to recipients from donated blood from asymptomatic donors who are silently infected with vCJD. It is not clear to me how one could go about answering this question. Experimental results published in 2004 (which cannot necessarily be directly extended to the real-life human situation) suggested that leuco-reduction would reduce infectivity in whole blood by around 42% (NHBT0033621). In a sheep blood transfusion experiment, the efficiency of transmission via RBCs was reduced from 18.9% to 6.9% by leuco-reduction (WITN5592014).

18. (b)"Can it eliminate the effects of the different genotypes of the

disease?"

I do not understand exactly what this question means. For example, what is meant by 'the different genotypes of the disease?' 'Genotype' refers to individuals, not diseases. There are different forms of CJD, but I think here you are interested in only one: vCJD? There are 3 different genotypes of individuals in relation to *PRNP*-129: we are all either MM, MV or VV. This genotype certainly has implications for prion disease, including vCJD but we do not know if this affects blood transmission, or, if it does, in what way. I do not know of any particular relevance of this in relation to leuco-reduction.

19. What role do you play in notifying patients of an exposure (or potential exposure) to vCJD?

The NCJDRSU has no role in the actual notification of individuals of an exposure or potential exposure. We have data from our surveillance and research that allow the identification of an exposure/potential exposure. This information is shared with other bodies that take the notification action.

Section 5: Scale of Exposure

20. A summary of any research studies or papers, reports, recommendations, look back exercises and databases that you are aware of, which have addressed the prevalence of the transmission of vCJD in blood and blood products.

The results of the TMER are discussed elsewhere (Paragraphs 11b, 16b, 21 & 23 of this statement and in WITN5592001, Paragraphs 10,11,12 & 22). The most recent publication of the TMER results was in 2016 (NCRU0000109_082).

21. Your view on the effectiveness of any look back studies, in particular TMER, to trace recipients of vCJD infected blood and blood products.

The basic mechanism of the TMER should be effective. If the NCJDRSU

identifies a case of vCJD and notifies this to the National Blood Services (NBS), along with any information the Unit has gathered from relatives about possible blood transfusion or donation, then it should be possible for the NBS to trace donors and recipients. As to the efficiency of the tracing, it would be necessary to ask the BTS. The names of recipients and donors traced are provided to the NCJDRSU and it should be possible to identify any cases of vCJD. It is difficult to see how any other system could be devised.

The question of asymptomatic infection is clearly more difficult since not all potentially relevant individuals have died, or if they have, not all had autopsies-as discussed at paragraph 27 b.

22. In an undated, report titled, "New Variant Creutzfeldt-Jakob Disease and the Risk", Royal College of Edinburgh/Royal College of Pathologists Joint Symposium (HSOC0015079), you stated that, '*Look back studies can yield useful information, but in view of the few known infected donors and long incubation time, these will take time. It should be borne in mind that there may be at least 80,000 people in the UK incubating nv-CJD, a proportion may well be blood donors.*" Is this number still correct, if not please set out the current figure and explain how it was calculated? Please set out what is known about the current vCJD incubation time?

You provide a document: HSOC0015079. The meeting referred to took place in May 1999, at an early stage of BSE/vCJD understanding. The meeting was reported by someone and their report is the document you provide. My first comment is that it reports me as saying something and it is not necessarily the case that it is exactly what I said. Unsurprisingly, I cannot recall exactly what I said at such a meeting over 22 years ago. However, the important point is that I quoted a figure concerning the possible number of cases of vCJD that would occur in the UK. At the time, there were many uncertainties and predictions were necessarily imprecise. Indeed, the figure I quote ranges from 75-80,000, which I think relates to an estimate made by modellers at the London School of Hygiene and Tropical Medicine. The huge range is really a way of saying that predictions are being based on very uncertain

knowledge. The point that was being made is that, although there was then no proven transmission of vCJD by blood, the existence of a number of infected people in the population that could donate blood, meant there was a potential risk. Anecdotal evidence (person X received blood and now has vCJD) or case-control studies could never provide solid evidence and some sort of 'look-back' study would be needed. The point I made, apparently, was that such a study would take time because of the long incubation period typical of prion diseases. In all honesty, the figures quoted here come from a time when far less was known about vCJD than is now known. In relation to your question as to the current figure, I presume you mean what is the prediction now of the number of UK individuals that will develop vCJD? The only two answers I can give are:

(i) Modelling was performed by Garske & Ghani in 2010 (WITN5592009). In this they estimated the following cumulative future numbers from 2010 to 2179 :
Total vCJD cases: 390 [95% Credibility Interval: 83-3000]
Total MM: 200 [20-2200]
Total MV: 160 [4-980]
Total VV: 13 [0-85]

Identifiable blood cases:
Total:17 [1-220]
MM:12 [0-160]
MV: 4 [0-57]
VV: 0 [0-5]

Given the observed data since 2010 up to 2021, one might be inclined to think that the lower part of the 95% credibility interval is more likely than the upper part.

(II) There have been estimates of the number of UK individuals who have asymptomatic infection (not necessarily the number who will develop vCJD), based on the analysis of surgical lymphoreticular specimens (mostly

appendix) (RLIT0000725). These estimates are discussed in the answer to your paragraph 24 below.

23. An outline of the system for recording the cause of death from vCJD infection from blood or blood products in the UK. Please provide your views on the accuracy of information captured about the cause of death and any areas of weakness or failures in this system to investigate, certify or record the cause of death where it was potentially linked to vCJD.

i. As it is posed, the question is confusing. Death does not result from vCJD infection as such (unless the vCJD infection becomes vCJD clinical illness). The recording of death cause is, in the first instance, a matter of local death certification. The death certificate cause may be amended if an autopsy determines a different cause. If an individual has been exposed to potential vCJD risk through blood/blood product and die of a non-vCJD cause, they are not known to be infected unless/until an autopsy provides evidence of this.

ii. Interpreting this question as referring to the system of the NCJDRSU's determination of the cause of death in those recipients of blood/blood products that have been determined as a potential risk because of the donor's vCJD:

iii. Recipients identified as at possible risk through blood are 'flagged' through NHS systems. In the event of a death, the NCJDRSU will subsequently obtain a copy of the Death Certificate. If the certification of death suggests prion disease or dementia then the NCJDRSU will, where possible, obtain medical records and review for any suggestion of vCJD. However, the time for obtaining autopsy consent will have long elapsed. If an autopsy has been performed, then attempts will be made to obtain the autopsy report and any available tissues.

iv. It is my understanding that flagging could result in Public Health England being notified of a death at the time of its occurrence and in a time period that could allow autopsy consent discussion.

v. It is also my understanding that the NPC (National Prion Clinic) has a cohort of 'at risk' individuals that may allow for prompt autopsy discussion in the event of a death.

vi. It should be understood that there have been significant Information Governance concerns around 'at risk' individuals and these have made it difficult to obtain consent for holding some information and in getting access to medical records.

vii. Even in those instances where a death is notified soon after its occurrence, with family consent to autopsy, it may be difficult to obtain an autopsy, depending on the location and local pathology services.

viii. Clearly, with issues around consent, information governance, sensitivity towards the 'at risk' person, and the practicalities of autopsy arrangements, it is not easy to ascertain whether an 'at risk through blood' individual has evidence of asymptomatic vCJD infection, although vCJD illness should be picked up through the national CJD surveillance system. An accurate determination of the rate of asymptomatic infection in 'at risk through blood' individuals is not possible with the present systems.

ix. To date, of the 67 recipients of blood from vCJD donors, 54 have died.

Of these 54: 3 had clinical vCJD and 1 had asymptomatic infection.

4 had autopsies reviewed by Professor Ironside with no evidence of vCJD or infection (2 were MM and 2 were MV).

A further 4 were reported as having had a Coroner's autopsy, with no diagnosis of vCJD, but no material was available for review.

42 had no autopsy or it is still unknown if an autopsy was performed (there is information that 2 of these were MM and 1 MV).

x. A study looked at possible missed cases of blood-related vCJD which was made possible following special permission from DH to review the relevant medical records (correspondence relating to this

has already been provided to the Inquiry). The relevant paper is: Gillies et al, 2009 (WITN5592015). In this study, the case records of 33 deceased recipients of vCJD donor blood were reviewed (representing 83% of known deceased 'at risk' recipients at that time). None of the 33 had medical records that suggested clinical vCJD but only 4 had survived for more than 5 years after transfusion (and so most did not survive long enough to develop clinical vCJD). This high short survival rate after transfusion is recognised since transfusions may be given for serious illnesses. This study could not, of course, eliminate the possibility of asymptomatic infection.

xi. Those deemed to be 'at risk' through blood products are not subject to the same process. Those deemed to be 'at risk' through haemophilia would be dealt with via the Haemophilia Centres Doctors Organisation Study (discussed at Section 38 in WITN5592001). Those at risk through treatment of Primary Immunodeficiency would be dealt with via the PID study (discussed at Section 37 in WITN5592001).

24. Please provide an estimate of the number of people infected with sub-clinical vCJD. You may be assisted by the email exchange in 2007 between Professor Bob Will and Dr Chris Verity (copied to you) in which it was noted that there may be 4,000 people who are infected with sub-clinical vCJD. Was this figure accurate in your view? If not, please explain why.

a. Firstly, it should be noted that there is a recognised difference between pre-clinical and subclinical as defined at paragraph 61a in WITN5592001. As pre-clinical cases are identified as such only after they finally become ill, I will interpret this question as referring to the number of instances of asymptomatic infection in the UK population. The Inquiry mentions documents: NCRU0000292_003, DHSC0020747_008, TSTC0000039 & TSTC0000049 which refer to this topic. In the first 2 of these, the number is explicitly stated as referring to 'pre- or sub- clinical' cases ie to asymptomatic infection. At this point in time, any estimate of the number of asymptomatic infections must be based on what have been termed the 'Appendix

Studies' (Appendix I, II and III); I know of no other way of estimating this number. The appendix studies are so-called because, although they looked at tonsil and appendix material, most of the studied material was appendix. These studies looked at routine surgical specimens and examined them for abnormal prion protein deposition of the sort that has been seen in vCJD, both in pre-clinical and clinical cases. The natural assumption being that such deposition indicates infection with BSE. The studies were anonymised and it is not possible to trace back to any individuals who had positive specimens. Because of the study design, it is known that any positive results did not come from known vCJD cases. In summary, the rates of a positive prion protein finding were:

'Appendix I': 237/million population

'Appendix II': 493/million population [95% CI: 282-801]

'Appendix III': results in line with 'Appendix II'

b. Taking the figure of 493/million, and a population of around 60 million, this equates to ~1:2000 of the population infected. This has been taken as the figure to use for Public Health purposes. However, the 493/million figure has a 95% confidence interval of 282-801, indicating that the rate could be lower or higher than 493. In addition, the figure is an extrapolation of the study findings to the whole population and is also the rate of a certain specific finding with the assumption that this indicates BSE infection. This assumption is entirely reasonable but the Appendix III study was designed to test this assumption by comparing the rates of prion protein positivity in appendices relating to 3 periods: before, during and after the accepted BSE dietary risk period (RLIT0000725). The study found no statistically significant difference in rates in all 3 periods. The possible interpretations being that either the positive prion protein finding did not, after all, necessarily indicate BSE infection or that the risk period of dietary BSE was wider than had been suspected. Either explanation is problematic.

c. In addition, even if around 1:2000 of the UK population is infected, it does not necessarily follow that they are all infectious, and if infectious,

infectious via blood or consistently infectious over a long time period. Certainly, there is a potential discrepancy between the assumed number of infected individuals on the one hand and, on the other hand, observed vCJD cases, the number of blood-related vCJD cases and the absence of any identified surgical vCJD transmission cases.

25.a Have the MV and VV genotypes since been attributed to vCJD/BSE in humans (subsequent to NCRU0000292_003)? Interpreting this question in relation to the quoted document, the answer is: yes. Definite vCJD has been identified in an MV individual (WITN7034010).

In addition, another case of vCJD, categorised as only 'possible' using the formal classification protocol, but considered a likely case, was found to be MV (WITN5592017).

25.b How likely is a future peak of vCJD disease among non-MM groups to occur? It has been considered likely that the codon 129 genotype will affect the susceptibility of an individual to BSE, the incubation period if clinical disease results and the likelihood that an infection might occur but be truly subclinical. The implications of this view is that (i) MV and/or VV waves will occur and later than the initial MM wave; (ii) MV and VV waves will probably be smaller than the MM one and (iii) subclinical infection might be commoner in MV and/or VV than in MM individuals. This view is supported by: (i) The fact that all the tested initial cases were MM; (ii) Observation of other prion diseases (such as Kuru or human-growth hormone CJD); (iii) experimental evidence (for example, Bishop M et al, 2006 (NHBT0008745_002). The paper by Garske and Ghani (Plos One 2010) gives predictions on the numbers of vCJD cases, by genotype and over time (2010-2179) (WITN5592009).

25.c Elsewhere it has been reported that there was a second case of c129 MV genotype and suspected vCJD but that this could not be confirmed as an autopsy was not performed. Are there other cases such as this that have potentially not been counted due to a lack of post mortem?

This is discussed above as the case without autopsy confirmation, with a formal classification of 'possible vCJD' but thought to be a likely case. There are no other instances of MV genotype that were thought likely to have had vCJD and none of VV genotype. However, not all vCJD cases have had codon 129 genotyping: of the 178 vCJD cases, 161 (90%) had codon 129 testing, so, in 17 definite/probable cases, the 129 genotype is unknown [genotyping required appropriate consent, with the opportunity for suitable sample collection and testing, which was not always available/given]. We have 4 cases that are classified as 'possible vCJD' and, of these 4, 3 were MM and 1 MV. The single MV case is the case referred to here as the 'second MV vCJD case'-classified as 'possible' but thought very likely to have had vCJD. The other 3 cases of possible vCJD are not thought to be very likely vCJD cases, but it is possible that they were, but they were all MM.

26. It is often said that there have been only four cases where blood transfusion or blood products have caused recipients to contract vCJD. Please confirm whether this is correct or not.

In relation to blood: I refer you to my answer to Q 16 above .

In relation to blood products, there is only one identified instance, relating to factor VIII, in which the recipient is considered to have contracted vCJD infection (but not vCJD disease) (HCDO0000799).

27. In 2014, Professor Bird stated that in respect of the Sixty-seven patients who had received blood or blood products from those who had become vCJD cases (TSTC0000049, page 8). "Only 18 have died, having been at least five years out from that exposure, but we have post-mortems on only eight of the 18….. Of those eight, half were positive for the abnormal prion, but fully to understand that we also need to know the age of the individual, the genotype and so on."

The European Medicines Evaluation Agency's Expert Workshop on Human TSE's and Plasma-Derived Medical Products, 15 May 2000, by L. Williamson. Meeting note states, 'Experience to date shows that all living

probable cases have turned out to be positive at post mortem' (NHBT0004096).

27a. If a patient tests positive for the abnormal prion protein through an autopsy, what category are they included within (Definite, Probable, Possible)?

The question, as it stands, seems confused. If a patient 'tests positive for the abnormal prion protein through autopsy', the interpretation of this depends on where in the body the abnormal prion protein is found, any other neuropathological findings, and the history of the patient prior to autopsy, including the cause of death.

If the patient had a neurological illness, prior to death, that is compatible with vCJD, and the brain shows characteristic pathological changes of vCJD, with abnormal prion protein being found in the brain or in the brain and in lympho-reticular tissue, then the case classification is of definite vCJD.

If the patient had no neurological illness (or a neurological illness quite definitely diagnosed as something other than CJD), and autopsy showed no vCJD changes in the brain, but there was abnormal prion protein of vCJD type found in lympho-reticular tissue, they would be classified as a case of subclinical vCJD infection.

The terms 'Probable' and 'Possible' refer to clinical diagnoses of vCJD in those individuals who do not come to autopsy. [The diagnostic classification criteria as used in TUK and international collaborative surveillance/research are provided as a separate document) (WITN5592002).

27b. It appears that in some circumstances, consent for an autopsy is not granted. How much does this affect the reliability of the current figures?

If this question relates to autopsies not undertaken in individuals who die following exposure to potential risk of vCJD through blood/blood products, then the effect is a straightforward one. If such individuals had a neurological

illness that suggested vCJD, they would be classified according to the standard protocol according to the clinical features and investigation results. If they had no brain biopsy and no autopsy, they could not be classified as definite vCJD. If they did not have a vCJD illness clinically, dying of some other cause, then the lack of an autopsy means that any asymptomatic vCJD infection that might be present (such as in lymphoreticular tissue) would not be detected. It is, therefore, *possible* that some cases of blood-related asymptomatic infection could be missed.

27c. Do you consider that a post-mortem examination should be made compulsory for patients who died due to probable vCJD as is done in other countries like Austria, which do not have as high a prevalence as the UK? Please set out the advantages and disadvantages of this in your view.

To reply to the question as to whether autopsy should be made compulsory in cases of probable vCJD, my answer is unequivocally negative. A diagnosis of 'probable vCJD' is in fact a highly probable diagnosis and I do not know of any case in whom this was the final clinical diagnosis, in which there was then an autopsy showing another illness. I am not sure what is the purpose of the question in that the group of people diagnosed with 'probable vCJD' are the one group in which one could argue that autopsy was not always necessary. I am also unsure of the policy in countries like Austria is precisely as stated in the question. Two much more important matters are: (i) the importance of autopsy in those who have been potentially exposed to infection (through blood, for example) and who die for other reasons (and are not considered to have clinical vCJD) and (ii) the importance of autopsy in neurologically ill people who have only possible vCJD. In (i), there is the possibility of finding evidence of asymptomatic infection as discussed in paragraphs 24 & 27a of this statement and as was found in investigation of blood/Factor VIII transmissions (NCRU0000109.082 & HCDO 0000799). In (ii) the diagnosis of possible vCJD could not be confirmed as vCJD nor excluded.

27d. Does the genotype affect the diagnostic test for the abnormal prion protein?

I am not entirely clear as to the meaning of this question.

If 'the diagnostic test for the abnormal prion protein.' refers to the detection of abnormal prion protein in tissues such as lymphoreticular tissue or brain, and the 'genotype' refers to the *PRNP*-129 polymorphism, then I am not aware of any differential detection capability dependent on whether the person is MM, MV or VV.

If 'the diagnostic test' refers to other tests used in diagnosis in life, most of these are either not related specifically to 'the abnormal prion protein' or are not diagnostic of vCJD (such as in the case of CSF RT-QuIC).

If 'the diagnostic test' refers to the blood tests that have been developed for vCJD clinical diagnosis, then I do not know of any evidence to suggest their results are dependent on the *PRNP*-129 polymorphism. If 'the diagnostic test' refers to the blood test that has been shown to detect 2 instances of pre-clinical vCJD, then, again, I know of no evidence to suggest its results are dependent on the *PRNP*-129 polymorphism. Of course, in these last two scenarios there has been no possibility of properly assessing the possible effect of the polymorphism on these tests.

27e. Are all the genotypes associated with vCJD included in the surveillance figures of recipients of blood/blood products?

Again, I am not entirely clear as the meaning of this question. The 'surveillance figures' do not include recipients of blood/blood products unless these recipients developed vCJD. In such an event, then the codon 129 genotype would be determined if possible, as in all cases of prion disease. If a recipient died from other causes and an autopsy was performed, then the codon 129 genotype would be determined as part of the autopsy process (as was done, for example, in the known instances of asymptomatic infection transmission). We do identify recipients through the TMER study but, if they were alive and well, these individuals are not included in 'surveillance figures' and we do not determine their 129 status. [However, I believe that there are

8 individuals, currently alive, who are included in a cohort at the National Prion Clinic with 129 status determined (4 MM, 4MV)].

27f. Are there other surrogate markers that can be used for these genotypes that cannot be deduced through a prion test?

I am afraid I do not understand this question, unless it is asking if there is another way of determining if any given individual is *PRNP*-129 MM, MV or VV, without undertaking a test to determine their 129 status. If so, then the answer is: No.

Section 6: Financial Assistance

The Inquiry states an interest into what financial assistance was given to those affected (individuals and their families) by vCJD as a result of blood/blood products.

I am not aware of any financial assistance that is given *specifically in relation to blood-related vCJD*. Financial assistance has been given to those affected by all forms of CJD; Compensation has been awarded to those affected by vCJD (dietary or blood-related).

The forms of financial assistance of which I am aware:

(i) Specific care costs through the Care Package (discussed at paragraph 6 in WITN5592001). I have had some responsibility for decisions made in relation to the Care Package but not currently.

(ii) Grants given by the CJDSN, as a charity aiming to help and support those affected by CJD. I have had a role in decisions made by the CJDSN Management Committee about the awarding of such grants.

(iii) Compensation given by the vCJD Trust. This compensation may be awarded in retrospect (after the affected individual's death) or during life to help support people.

29. Involvement in discussions arising from consultations with representatives of families affected by vCJD leading to the creation of the vCJD Trust.

I do not recall involvement of the sort specified in the question. I was a member of the Human BSE Foundation (HBSEF) committee (as a Medical Advisor) for a period of time. I have been a long-time member (and current Chair) of the CJDSN Management Committee. Both of these organisations are composed mainly of family members affected by CJD (in the case of the HBSEF, vCJD and, in the case of the CJDSN, all forms of CJD, including vCJD). As such, I have been involved in discussions that have included compensation matters.

My specific involvement with compensation has been as Specialist Advisor to the vCJD Trust.

30. Did you provide advice to the vCJD Trust as to the different levels of care a person might expect to need at different stages of the disease?

I gave a presentation to the vCJD Trust Board in order to familiarise the members of that Board with the background to vCJD.

Otherwise, my role has been simply to provide specific information about individuals who are part of a claim to the Trust. The two specific items are: (i) the diagnosis of vCJD expressed in terms of the individual having vCJD (or not) on the balance of probability and (ii) whether or not the individual concerned lived in the UK during the defined risk period. Both of these data being available through the routine surveillance data collected by the NCJDRSU.

30a. How was this advice commissioned from you? See below

30b. What form did the advice take? See below

30c. What did the advice say? See below

30d. Was the advice intended to set down guidance applicable to all cases? If so, please explain the basis upon which guidance could be given. If not, were you aware that it may have been used in this way by the vCJD Trust? See below

In relation to 30 a-d, I do not recall being asked to give specific advice on the level of care individual patients may require. I presume-but do not recall whether it was so-that the sort of care requirements that might be met in general were part of my introductory presentation to the Board.

31. Please provide your view as to whether the Trust has been successful in delivering its objectives with your reasons why.

As far as I am aware, the Trust has provided compensation to families in the manner intended, to families after death and, in life, financial awards where appropriate and needed.

Section 7: Other issues

I have nothing specific to add to the above.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed _____ GRO-C _____

Dated _____18.04.22_____

Table of exhibits:

Reference	Title	Exhibit no.	Relativity URN
*	A copy of the current CJD Diagnostic Criteria supplied as a separate document.	WITN5592002	
1	Gill O N et al. Prevalence in Britain of abnormal prion protein in human appendices before and after exposure to the cattle BSE epizootic. Acta Neuropathologica 2020; 139(6):965		RLIT0000725

2	Mok T et al. Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at PRNP Codon 129. NEJM 2017. DoI:10.1056/NEJMMc1610003.		WITN7034010
3	Edgeworth J A et al. Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay. Lancet 2011; 377: 487–93		NHBT0033626
4	Concha-Marambio L et al. Detection of prions in blood from variant Creutzfeldt-Jakob disease. Sci Transl Med 2016; 8(370):370ra183.	WITN5592003	
5	Bougard D et al. Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease. Sci. Transl. Med 2016; 8, 370ra182.	WITN5592004	
6	Davidson L et al. Variant CJD and blood transfusion: are there additional cases? Vox Sang 2014 107:220	WITN5592005	
7	Urwin P J M et al. Creutzfeldt–Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. Vox Sanguinis 2016; 110, 310–316.		NCRU0000109_082
8	McCutcheon S et al. All Clinically-Relevant Blood Components Transmit Prion Disease following a Single Blood Transfusion: A Sheep Model of vCJD. PLoSOne 2011; 6(8): e23169.	WITN5592014	
9	Peden A. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia (2010), 16, 296–304.		HCDO0000799
10	Gillies M et al A retrospective case note review of deceased recipients of vCJD-implicated blood transfusions2009 Vox Sang 2009; 97:211–218.	WITN5592015	
11	The House of Commons Science and Technology Committee Report, “After the Storm?” HC327 incorporating HC1990 Session 2013-14.		**TSTC0000052**
12	Cooper J K et al. Evaluation of a test for its suitability in the diagnosis of variant Creutzfeldt–Jakob disease. Vox Sanguinis (2013) 105, 196–204.	WITN5592016	
13	Gregori L et al. Estimation of variant Creutzfeldt-Jakob disease infectivity titers in human blood. Transfusion. 2011. 51(12): 2596-602		NHBT0033621
14	Garske T and Ghani AC. Uncertainty in the Tail of the Variant Creutzfeldt-Jakob Disease Epidemic in the UK. PLoSOne. 2010; 5(12):e15626	WITN5592009	

15	Kaski D et al. Variant CJD in an individual heterozygous for PRNP codon 129. Lancet 2009; 374: 2128	WITN5592017	
16	Bishop M et al Predicting susceptibility and incubation time of human-to-human transmission of vCJD. Lancet Neurol 2006; 5: 393–98.		NHBT0008745_002
17	The National Creutzfeldt-Jakob Disease Research & Surveillance Unit Witness Statement to the Inquiry.	WITN5592001	

Schedule of Relativity documents referred to in the statement

	Description	Document Date	Relativity URN
1	Minutes of Transfusion Medicine Epidemiology Review meeting on 29 March 2011 at the West End Donor Centre, re: tracing and notification of recipients of donors to vCJD cases.	29/03/2011	NCRU0000109_014
2	Letter from Richard Knight, Consultant Neurologist of the National Creutzfeldt-Jakob disease Surveillance Unit, to Patricia E Hewitt, Lead Consultant in Transfusion Microbiology of the National Blood Service, regarding a letter from Professor Doyal and the author's opinion on notification of patients at risk of vCJD (through blood).	25/01/2000	NHBT0004320
3	Report, "New Variant Creutzfeld-Jakob Disease and the Risk", Royal College of Edinburgh/Royal College of Pathologists Joint Symposium.	undated	HSOC0015079
4	Email from Richard Knight, to Cerity Christopher, re: PIND study renewal propositions.	17/07/2007	NCRU0000292_003
5	Minutes of the National Creutzfeldt-Jakob Disease Surveillance Unit (CJDSU) Steering Group scientific meeting, 24 June 2005, Department of Health (DOH).	24/06/2005	DHSC0020747_008
6	House of Commons Science and Technology Committee Oral evidence regarding whether prions currently pose the most significant risk to the UK blood supply.	26/03/2014	TSTC0000049
7	Written evidence submitted by the National CJD Research & Surveillance Unit in their capacity as a partner in the TMER study that identified the known	01/01/2014	TSTC0000039

	cases of actual blood and blood product prion disease/infection transmission.		
8	Letter from Goodmans Solicitors, to The Secretary of State for Health, re: The Variant Creutzfeldt Jakob disease trust.	05/10/2007	DHSC0041230_075

Appendix 1: List of Publications

I have listed all my publications relating to prion disease.

- **Transmissible Dementia: Clinical Aspects** Knight R In: Degenerative Neurological Disease in the Elderly Griffiths RA and McCarthy ST (Eds) Chapter 12: 109-118 Wright, Bristol. 1987
- **Creutzfeldt-Jakob disease in England and Wales 1980-1984 : a case-control study of potential risk factors.** Harries-Jones R, Knight R, Will RG, Cousens S, Smith PG, Matthews WB Journal of Neurology, Neurosurgery and Psychiatry 1988; 51 : 1113-1119.
- **Creutzfeldt-Jakob disease** Knight R British Journal of Hospital Medicine 1988; 41 : 165-171
- **Creutzfeldt-Jakob disease.** Knight R. British Journal of Hospital Medicine 1989; 41: 165-171 1988
- **Geographical distribution of cases of Creutzfeldt-Jakob disease in England and Wales 1970-1984** Cousens SN, Harries-Jones R, Knight R, Will RG, Smith PG, Matthews WB Journal of Neurology, Neurosurgery and Psychiatry 1990; 53 : 459-465
- **Creutzfeldt-Jakob disease** Knight R Postgraduate Doctor 1990; 13 : 500-508
- **Slow Virus Infections** Knight R In: Clinical Neurology. Oxbury J and Swash M (Eds) Section 18: 819-834 Churchill Livingstone, Edinburgh 1991 [Book Chapter]
- **Creutzfeldt-Jakob Disease and blood transfusion** Esmonde T, Will R, Slattery J, Knight R, Harries-Jones R, de Silva R, Matthews WB Lancet 1993; 341 : 205-207.
- **Creutzfeldt-Jakob Disease** Knight R In: Developments in Psychiatry 1982-1994. Ed K Katz: 305-317 Mark Allen 1996
- **Creutzfeldt-Jakob disease in the elderly** De Silva R, Findlay C, Awad I, Harries-Jones R, Knight R, Will R Postgraduate Medical Journal 1997 73:557-559
- **Reporting of suspect new variant Creutzfeldt-Jakob disease** Will RG, Knight R, Zeidler M, et al Lancet 1997 394 (Letter)
- **Creutzfeldt-Jakob disease: Clinical features, epidemiology and tests** Knight R Electrophoresis 1998; 19: 1306-1310
- **The new variant form of Creutzfeldt-Jakob disease** Richard Knight, Gillian Stewart FEMS Immunology and Medical Microbiology 1998 21 97-100
- **The Diagnosis of Prion Diseases** Knight RSG Parasitology 1998 117:S3-S11
- **New variant Creutzfeldt-Jakob Disease is more common in Britain than elsewhere** Ironside JW, Knight RSG, Will RG, Smith PG, Cousens SN BMJ 1998; 317:352 (Letter)
- **New variant Creutzfeldt-Jakob disease: Diagnostic features on MRI with histopathological correlation** Collie DA, Sellar RJ, Ironside J, Zeidler M, Stewart G, Knight R, Will RG Proceedings of ASNR, AJNR(Supplement) 1998 20: 139 [ABSTRAct]
- **Geographical distribution of variant CJD in the UK (excluding Northern Ireland).** Cousens SN, Linsell L, Smith PG, Chandrakumar M, Wilesmith JW, Knight RSG, Zeidler M, Stewart G, Will RG. Lancet 1999 353: 18-21
- **Psychiatric features of new variant Creutzfeldt-Jakob disease** Will RG, Stewart G, Zeidler M, Macleod M, Knight RSG Psychiatric Bulletin 1999 23: 264-267
- **New variant Creutzfeldt-Jakob disease** MacLeod MA, Knight RSG Cattle Practice 1999 7(2): 211-214

- **Deaths from variant Creutzfeldt-Jakob disease** Will RG, Cousens SN, Farrington CP, Smith PG, Knight RSG, Ironside JW Lancet 1999; 353: 979 (Letter)
- **Routine tonsil biopsy for diagnosis of new variant Creutzfeldt-Jakob disease is not justified** Zeidler M, Knight RSG, Stewart G, Ironside JW, Will RG, Green AJE, Pocchiari M BMJ 1999 318: 538 (Letter)
- **Clinical Features of nvCJD** MA Macleod, Knight R, Stewart G, Zeidler M, Will R. European Journal of Neurology 1999 6(3) :26-27
- **The Relationship between New Variant Creutzfeldt-Jakob Disease and Bovine Spongiform Encephalopathy** Knight R. Vox Sanguinis 1999; 76: 203-208
- **Extent of misclassification of death from Creutzfeldt-Jakob disease in England 1979-96: retrospective examination of clinical records**. Majeed A, Lehmann P, Kirby L, Knight R, Coleman M BMJ 2000 320: 145-147
- **The diagnosis of new variant Creutzfeldt-Jakob disease**. Will RG, Zeidler M, Stewart G, Macleod MA, Ironside JW, Cousens SN, Mackenzie J, Estibeiro K, Green AJE, Knight RSG Annals of Neurology 2000 47:575-582
- **The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease** Martin Zeidler, Robin J Sellar, Donald A Collie, Richard Knight et al Lancet 2000 355:1412-1418
- **Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease**. Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, Bernheimer H, Cardone F, Delasnerie-Laupretre N, Cuadrado Corrales N, Laadogana A, Bodemer M, Fletcher A, Awan T, Ruiz Breomon A, Budka H, Laplanche JL, Will Rg, Poser S. Neurology 2000. 55: 811-5
- **Incidence of variant Creutzfeldt-Jakob disease in the UK** Andrews NJ, Farrington CP, Cousens SN, Smith PG, Ward H, Knight RSG, Ironside JW, Will RG. Lancet 2000 356:481-482 (Research Letter)
- **Therapeutic possibilities in CJD: patents 1996-1999** Knight RSG. Exp. Opin. Ther. Patents 2000 10 (1):49-57
- **Tetrapyrroles as anti-amyloidogenic drugs in the treatment of transmissible spongiform encephalopathies.** Head MW & Knight R. Exp. Opin. Ther. Patents. 2000 10: 1461-1464
- **Prion-related diseases and the central nervous system** Knight R, Will RG In: Neurosurgery: The Scientific Basis of Clinical Practice. Crockard A, Hayward R, Hoff JT (Eds) Vol 2: 807-814 Blackwell Science, Oxford 2000
- **Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease**. Zerr I, Pocchiari M, Collins S, Brandel J-P, de Pedro Cuesta J, Knight RS et al. Neurology 2000;55(6):811-5.
- **Raised Concentration of brain specific proteins in patients with sporadic and variant CJD** AJE Green, Thompson EJ, Zeidler M, Stewart G, Mackenzie J, Macleod MA, Knight R, Will RG JNNP 2000; **69**: 419 [abstract]
- **Sensory Features of variant Creutzfeldt-Jakob disease** Macleod MA, Knight R, Stewart G, Zeidler M, Will R,. JNNP 2000 69: 413-414 [abstract]
- **Geographical Distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000** Simon Cousens, PG Smith, H Ward, D Everington, RSG Knight, M Zeidler, G Stewart, EAB Smith-Bathgate, M-A Macleod, J Mackenzie, RG Will. Lancet 2001 357: 1002-07
- **Use of 14-3-3 and other brain-specific proteins in CSF in the diagnosis of variant Creutzfeldt-Jakob disease.** AJE Green, EJ Thompson, GE Stewart, M Zeidler, JM McKenzie, M-A MacLeod, JW Ironside, RG Will, RSG Knight. JNNP 2001;70: 744-748
- **Variant Creutzfeldt-Jakob Disease** Andrea Lowman, Richard Knight, James Ironside Practical Neurology 2001; 1: 2-13
- **Creutzfeldt-Jakob Disease: A Protein Disease** Knight R Proteomics 2001; 1: 763-766
- **MRI of Creutzfeldt-Jakob: Imaging Features and Recommended MRI Protocol** DA Collie, RJ Sellar, M Zeidler, ACF Colchester, R Knight, RG Will Clinical Radiology 2001; 56: 726-739

- **Human Prion Diseases: Cause, Clinical and Diagnostic Aspects** Knight R, Collins S. In: Prions: A challenge for Science, Medicine and Public Health System Contributions to Microbiology Vol 7: 68-92 Eds: Rabenau HF, Cinatl J, Doerr HW. Karger, Basel, 2001 [Book Chapter]
- **FLAIR MRI in sporadic Creutzfeldt-Jakob disease** M Zeidler, DA Collie, MA Macleod, RJ Sellar, R Knight Neurology 2001 56: 282 (Letter)
- **Misleading results with the 14-3-3 assay for the diagnosis of Creutzfeldt-Jakob disease. AJE** Green, RSG Knight, MA MacLeod, A Lowman, RG Will. Neurology 2001 56: 986 [LETTER]
- **Epidemiology of vCJD** Knight R Infus Ther Transfus Med 2001; 28(Sonderheft 1): 51-52 [Abstract]
- **Increased CSF levels of Prostaglandin E_2 in variant CJD** Luisa Minghetti, Franco Cardone, Maria Puopolo, Guilo Levi, Alison Green, Richard Knight, Maurizio Pocchiari. Neurology 2002; 58: 127-9
- **First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note of early psychiatric and neurological features.** Michael D Spencer, Richard SG Knight, Robert G Will. BMJ 2002 342:1479-82
- **Apolipoprotein E and other cerebrospinal fluid proteins differentiate antemortem variant Creutzfeldt-Jakob disease from antemortem sporadic Creutzfeldt-Jakob disease** Leila H Choe, Alison Green, Richard SG Knight, Edward J Thompson, Kelvin H Lee. Electrophoresis 2002 23: 2242-2246
- **14-3-3 in the cerebrospinal fluid of patients with variant and sporadic Creutzfeldt-Jakob disease measured using capture assay able to detect low levels of 14-3-3 protein** Alison JE Green, Sanja Ramljak, Werner EG Müller, Richard SG Knight, Heinz C Schröder. Neuroscience Letters 2002 324: 57-60
- **Sensory features of variant Creutzfeldt-Jakob disease.** MA Macleod, GE Stewart, M Zeidler, R Will, R Knight. J Neurol 2002 249:706-711
- **Mutations of the prion protein gene. Phenotypic Spectrum.** Kovacs GG, Trabattoni G, Hainfellner JA, Ironside JW, Knight RSG, Budka H. J Neurol 2002: 249: 1567-1582
- **Probable Variant Creutzfeldt-Jakob Disease in a US Resident-Florida, 2002** S Wiersma, S Cooper, R Knight, AM Kennedy, S Joiner, E Belay, LB Schonberger MMWR 2002 51: 927-929
- **Clinical Features of Variant Creutzfeldt-Jakob Disease.** Colm Henry and Richard Knight Rev.Med.Vir. 2002; 12:143-150
- **Neuropathology of variant Creutzfeldt-Jakob disease.**James W Ironside, Mark W Head, Linda McCardle, Richard Knight. Acta Neurobiol. Exp. 2002, 62:175-182
- **Epidemiology of variant CJD.** Knight R In: Advances in Transfusion Safety Developments in Biologicals Volume No 108: 87-92 Brown F, Seitz R (eds) Karger, Basel, 2002.
- **CJD: The Promise of Treatment.** Knight R (Editorial) The British Journal of Infection Control 2002 3:4
- **Different faces wearing the same expression: is there a core neuropsychological deficit in sporadic CJD?** Knight R JNNP 2002 73:613-614 (Editorial Commentary)
- **New variant Creutzfeldt-Jakob disease: The critique that never was.** Will RG, Knight RSG Ward HJT, Ironside JW. BMJ 2002 325:102
- ***Vaccines and Creutzfeldt-Jakob disease (CJD)** Ward H, S Cousens, D Everington, A Lowman, B Smith-Bathgate, M Leitch, S Cooper, R Knight, P Smith, R Will International Conference on Transmissible Spongiform Encephalopathies, Book of Abstracts, 2002, p. 57
- **The pulvinar sign and diagnosis of Creutzfeldt-Jakob disease.** Summers DM, D A Collie, R J Sellar, M Zeidler, R Knight, R G Will, J W Ironside Neurology 2002; 59: 962
- **Deaths from variant Creutzfeldt-Jakob disease in the UK**
- Andrews NJ, Farrington CP, Ward HJT, Cousens SN, Smith P, Molesworth AM, Knight RSG, Ironside JW, Will RG. Lancet 2003 361:751-52
- **Diagnosing Variant Creutzfeldt-Jakob Disease with the Pulvinar Sign: MR Imaging Findings in 86 Neuropathologically Confirmed Cases.** DA Collie, DM Summers, RJ Sellar,

JW Ironside, S Cooper, M Zeidler, R Knight, R Will. American Journal of Neuroradiology 2003 24: 1560-1569

- **The normal population distribution of *PRNP* codon 129 polymorphism.** Marja H Nurmi, Matthew Bishop, Lisa Strain, Francesca Brett, Christopher McGuigan, Michael Hutchison, Michael Farrell, Reijo Tilvis, Satu Erkkilä, Olli Simell, Richard Knight, Matti Haltia. Acta Scand Neurol 2003 108:374-378
- **The Differential Diagnosis of Creutzfeldt-Jakob Disease: Data from the National CJD Surveillance Unit.** Cooper SA, Heath CA, Knight R. JNNP 2003 74:1454-5 [Abstract]
- **Prion Diseases** Richard Knight and Bob Will In: Course and Treatment of Neurological Disorders Second Edition, Chapter 54: 707-720 Eds. Brandt T, Caplan LR, Dichgans J, Diener HC, Kennard C Academic Press, 2003 [Book Chapter]
- **An Overview of the care issues for Creutzfeldt-Jakob Disease.** Belinda Weller, Richard Knight, Robert Will European Journal of Palliative Care 2003 10: 5-8
- **Variant CJD: the present position and future possibilities.** Knight R International Journal of Paediatric Otorhinolaryngology 2003,67S1,S81-S84
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- **Heterogenity in the abnormal prion protein isoforms in the brains of sporadic but not variant Creutzfeldt-Jakob disease patients.** Green AJE, T M Sivtseva, A P Danilova, V L Osakovsky, V A Vladimirtsev, M Zeidler, R S Knight, F A Platonov, A Shatunov, V S Alekseev, V G Krivoshapkin, C L Masters, D C Gajdusek, Head MW, T J R Bunn, M Bishop, R Knight, R G Will, J W Ironside. Conference 2003
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- **Prion Diseases.** Richard Knight R, & Bob Will Neurology in Practice Issue 13 NNP 2004; 75 (Suppl 1): i36-i42
- ***Prion Diseases.** Knight R Vox Sanguinis 2004 87(Suppl 1) S104-S106 [REVIEW]
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- **A case control study of sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of clustering.** Linsell L, S N Cousens, P G Smith, R S G Knight, M Zeidler, G Stewart, R de Silva, T F G Esmonde, H J T Ward, R G Will Neurology 2004; 63: 2077-2083
- ***Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion.** Llewelyn CA, P E Hewitt, R S G Knight, K Amar, S Cousens, J Mackenzie, R G Will Lancet 2004; 363: 417-421
- **Evaluation of urinary PrPSc as a diagnostic test for sporadic, variant, and familial CJD.** Head MW, Kouverianou E, Taylor L, Green A, Knight R Neurology 2005; 64:1794-1796 [PRP]
- **A case-control study investigating dietary risk factors for variant CJD.** Heath CA, Cooper SA, Murrat K, Everington D, Smith-Bathgate B, Leitch M, Smith P, Cousens SN, Knight RSG, Ward HJT. JNNP 2005 76(1): 150 [Abstract]
- **Creutsfeldt-Jakob Disease associated with human dura mater-experience from UK surveillance.** Heath CA, Murray KL, Yull HM, Head M, Will RG, Knight RSG. JNNP 2005 76(9): 1318 [Abstract]
- **Genetic Prion Disease: the EUROCJD experience.** Kovacs GG, Puopolo M, Ladogana A, Pocchiari M, Budka H, van Duijn C, Collins SJ, Boyd A, Giulivi A, Coulthart M, Delasnerie-

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