D-Gen

D-Gen Limited

Confidential

By email

Dr Roland Salmon
c/o ACDP Secretariat
Public Health England
61 Colindale Avenue
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27 August 2015

Dear Roland

Thank you for your email of 24 July, following our earlier telephone conversations, setting out a possible pathway to a prevalence study of vCJD in UK human blood. This has now been discussed by the D-Gen board.

D-Gen continues to be prepared in principle to make its assay available for a comparative study of blood from BSE-exposed (UK) and unexposed (US) populations which would provide an initial estimate of prevalence of detectable prionaemia in the UK population and, importantly, would be the only way at present of determining whether the assay can detect asymptomatic human vCJD carriers. However, the D-Gen board is growing increasingly concerned that its comments and suggestions for planning a prevalence study are being ignored. Furthermore, from D-Gen's viewpoint, there appears to be no coordinated mechanism or process for progressing towards meeting the Select Committee's view that a prevalence study is required urgently. Indeed, the focus by members of the ACDP TSE Sub Group on animal model results appears to have prevented key aspects of a study being considered and resolved.

We have noted the Select Committee's comments on the protracted decision making processes, particularly as experienced by Prometic for its prion filter, and we have concluded that it would not be advisable for D-Gen to continue to be involved in this undefined and open-ended process for deciding whether and how a prevalence study should proceed. Given the multiplicity of committees and bodies and several potential conflicts of interest, we do not believe that there is a realistic prospect of a prevalence study being undertaken using our assay unless there is a clearly defined and streamlined process for planning, approving and project managing such a study.

We reiterate the statement in my letter of 13 May to Dr Lorna Williamson that, before entering into any arrangements for the use of the assay, we would wish to obtain clarity on the plan/protocol and approval process for the human blood study. You mentioned on the telephone that the decision whether to proceed with a prevalence study would ultimately be

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taken by the Department of Health. Presumably this decision would be based on a recommended proposal which addressed the relevant issues including costs and timetable so that approval by the DoH could result in the study commencing without significant delay. We understand that a number of issues have been discussed by committees and other bodies since the Select Committee's recommendation in July 2014 but it appears from your email that an outline of the elements of the prevalence study has not yet been formulated. As so little clarity has emerged since my letter, D-Gen is unable to consider at the present time any arrangements with NHSBT as referred to in Dr Williamson's letter of 23 July.

We continue to consider that our prototype assay in its current format is suitable for a prevalence study whose purpose would be to determine whether the assay can detect human carriers and to provide initial epidemiological data.

In its written evidence to the Select Committee, Public Health England stated that "All technical experts who have considered the matter are aware that the blood test requirements for an unlinked anonymous prevalence survey need not be as rigorous as a blood test for strengthening blood safety (i.e. screening and excluding blood donations)." PHE stated in its November 2014 paper (ACDP_TSE_03_P14) that D-Gen's assay is suitable in principle for an anonymous prevalence study in terms of its reported sensitivity and specificity (70% and 100% respectively).

As regards its performance, the assay has detected vCJD prion proteins in human patient blood and its analytical sensitivity in detecting vCJD brain in human blood is several orders of magnitude greater than the sensitivity required by the EU Common Technical Specifications for vCJD screening assays. Furthermore the assay has demonstrated specificity of 100% in 5,000 US donors which would satisfy the CTS acceptance criterion of 99.5%. All these data have been published in highly respected peer reviewed journals.

In the light of the above, we are at a loss to understand the apparent difficulty of certain members of the TSE Sub Group in accepting the assay's performance as being satisfactory for a prevalence study.

When the CJD Resource Centre Oversight Committee was established in 2007, it was against the background of multiple assay developers seeking significant quantities of scarce vCJD patient blood samples. It was clearly necessary to limit access to those samples and a protocol was developed involving use of animal models as part of the evaluation process for eventual access to these valuable and irreplaceable patient samples. However, our assay has already demonstrated detection in patient blood and has been developed well beyond the scope of the Oversight Committee's historical evaluation process. The hurdle of demonstrating performance on animal samples prior to gaining access to human samples is therefore irrelevant.

You enquired about studies using the assay with sheep and mice experimentally infected with BSE but I have been informed by the MRC Prion Unit that it has not undertaken such studies. The assay method would require lengthy re-optimisation and modification for use in each animal model and this would cause considerable further delay. However, for the reasons mentioned in previous letters, we do not consider that animal data, irrespective of whether it showed positive or negative results, would in any case provide useful evidence about presymptomatic detection in humans which could only be established with human samples.

Concerningly, you introduced in your email a further suggestion by some TSE Sub Group members of a comparison between results from our assay and PMCA-based assays. We

are not clear what this would involve or how it would be helpful, other than that PMCA may have a role as a confirmatory assay in the prevalence study.

Given the recent experience with the appendix studies and the planning work for a blood study undertaken by the Prion Unit several years ago, we believe that the preparation of a proposal for a blood prevalence study should be entirely straightforward. We hope that a process can be adopted which enables this to be done expeditiously. I appreciate that the ACDP TSE Sub Group is not the only official participant in this matter but I should make it clear that D-Gen is unlikely to wish to continue discussions unless it has a substantial reassurance that a realistic way forward can be established rapidly.

I would be happy to have a further conversation with you to discuss how this could be progressed and I look forward to hearing from you.

Yours sincerely

GRO-C

Bernard Jolles

Director

Cc Dr Lorna Williamson

Dr Philip Minor