Written Evidence from Prof Garth Cruickshank (BCCR0002) April 2021

Response to Questions Posed by House of Commons Petitions Committee concerning how brain tumour research and patient care has changed since 2016

1. Has the work of the Tessa Jowell Brain Cancer Mission, and protected funding from NIHR and CRUK, led to a more favourable research environment for brain tumour research (in particular basic/discovery research)? Is this being felt on the ground by the research community, in particular when it comes to the availability of research funding?
   Yes and Yes but the funds are coming through very slowly. Only a small proportion of the £40m promised has been released. (BTR press releases) (See further comments in item 4 as to how this might be addressed) Others may be able to give more specific data on this issue than I am able to provide – perhaps comparing 2019,20,21 defined Brain Tumour Grant giving totals before vs after the TJ initiative. This might provide some objective index to assess by.

2. What progress do you feel has been made on improving awareness of brain tumours among GPs and other healthcare professionals since 2016, and reducing misdiagnosis and diagnosis in an emergency setting?
   My Understanding from Prof David Walker (Nottingham: Paediatric Oncologist)) that in the areas where the HeadSmart [i] project has been applied the effect has been marked at encouraging all stakeholders in childrens' health to be aware of the key signs that may indicate a child has a brain tumour. The Head Smart team have expanded their work and have been successful at sustaining the impact of their approach.
   This kind of thinking needs to be rethought to be as effective in adults, where delays in diagnosis are key areas of patient complaint. In addition, delays in diagnosis for patients with malignant tumours may exclude them from any useful therapy[ii]. An issue worth exploring here is to consider the threshold in Primary Care for pursuing a definitive head scan (MRI/CT) to diagnose. There are two issues here one is cost. Put bluntly -How many negative scans can we afford to find a positive one? This is a real cost issue and one that has not been settled resulting in very different policies across CCT's throughout the UK. Add to this current waiting times and Covid serial access issues, then imaging access for suspected brain tumour is likely to worsen. For individuals of course, the value of negative (tumour free) scan has never been quantified but must be enormous if they are worried. Could we define a better threshold for access to imaging to help GP's . The last NICE guidelines on cancer diagnosis with reference to brain tumours was too long and unhelpful. [iii]The success of HeadSmart was on its simplicity and direct applicability. Hence with adults although some may present with a seizure or sudden deficit necessitating hospital admission (10%), most do not. They often have a variety of symptoms with again only a small proportion having headache and that often late on in the disease. One suggestion has been to refer for a scan any one who has more than one neurological symptom or sign especially if they are persisting more than say ten days. This very clear and would need costing out to see if as a criterion it would lower the threshold enough to allow us to accept a positive scan rate of between 2 and 5% as suggested by CRUKs policy documents. *It is important to realise that most brain tumour patients (`60%) still receive their diagnosis form a scan carried out in A and E indicating a key area of weakness in Primary Care practise.*

3. How has the situation for an early career researcher looking to specialise in brain tumour research changed since 2016? Are you aware of more researchers now entering or intending to pursue a long-term career in brain tumour research?

   Most of those *non -clinical* scientists initial entering the sphere of brain tumour research do so passively either by default based on the area being included in a life science or cancer research course or program, or as a more active response to being exposed to a friend or family member having suffered from a brain tumour. The evidence for this is derived from statements from those currently in employment.

   For those *non-clinical* who have had some exposure to brain tumour research, who wish to progress, and have evidence of this through qualifications achieved the openings are however limited and hence retaining these researchers is an ongoing issue, particularly where they have gained the skills to be effective in brain tumour research. The basic requirements for entry into the commercial or indeed a more secure academic pathway include **at least** a PhD in Cancer Biology or similar discipline, with a specific focus on glial cancers. A Strong academic publication record is usually very important and/or demonstrable research expertise and or in a commercial setting, and additional experience of translational clinical research is considered very important for more senior posts to ensure researchers are up to speed with the current complex regulatory environment. All posts are now subject to open advertising and in an information request to *New Scientist* reveals only six jobs at a post doctoral level from either commercial or academic institutions in a two years advertising linked to the search term 'brain tumours' or 'glioma'.

   All (clinical) neurosurgical and many neurological post graduate clinical trainees will be exposed to patients with brain tumours. They will attend MDT meetings and be aware of current national and local portfolio clinical trials. (NCRI [iv]) A proportion will wish to pursue neuro-oncology as a subspeciality and will hence be expected to get involved in ongoing research projects or to consider doing a research degree often to PhD level to underwrite their specialisation. Many post CCT trainees will seek to demonstrate specialist interest or expertise through a one or preferably two year Fellowship post at a national or internationally recognised brain tumour research/clinical centre. Here they would be expected to contribute considerably to ongoing research projects.

4. Do the new Tessa Jowell Centres of Excellence offer an effective way to concentrate brain tumour clinical and research expertise? What further support could Government offer to help them drive progress in brain tumour care and research?

   There is no doubt that the TJ initiative overall has enlivened and invigorated the debate about brain tumour research in the UK. Those who have been encouraged to join in the debate anew, have themselves had to face the realisation that a treatment for brain tumours will be difficult to come by and that a much more integrated and professional national effort is required if we are to make inroads into the issues.[v] Having said that we are seeing a slow growth in critical research mass in many centres that is aimed at the brain tumour research. It is important to recognise that the TJ initiative with respect to Centres of Excellence had been very warmly received and those centres recently named are rightly proud to have been selected. The aim is to get all clinical units dealing with brain tumours into the fold as such Centres. One of the several issues with these Centres is to recognise that unless patients are receiving the very best treatment as a baseline then attempting complex expensive clinical trials will fail both in process and outcome. Patients on trials do better and it is the best units that do these the best – a finding that CRUK has alluded to frequently.

   Note that the emphasis with the TJ Centres is on clinical delivery of care not research but as stated above this underpins good trails work. Basic Brain Tumour research is carried out in

many sites in the UK. The bulk of research is carried out in academic units supported by competitive grants that have limited lifetime. Good units can sustain several concurrent grants that sustain an overall effort. Each grant is usually a salary and hence researchers live a fairly precarious existence on such funding unless they can land an academic post. Even these are subject to the rule of 'publish or perish' . Some centres of research have local or endowment based incomes to sustain them. Brain Tumour Research (Charity) has developed a basic research 'Centre' model that identifies with local and national fundraising initiatives but seeks to sustain group of researchers junior to senior on a regularly peer reviewed program of important brain tumour research. This model not only helps nurture and develop new researchers but also because it is embedded in a university is enabled to lever additional funding not only from specific grants but also from institutional research theme support as well as from BTR donation.

Thus whilst the TJ initiative is warmly welcomed. We need also to see a real shift in the proportion of funding attributable to Brain Tumour research from CRUK in particular but also NCRI, MRC etc To this end the integration of effort to supply high quality grant applications must also be bought into by these authorities much more actively than in the past. The recent initiative on 'Repurposing of Drugs' [vi]is perhaps a first signal that on these evolving responsibilities for grant giving authorities lies the future of brain tumour research.

5. Are there any other developments in the care of and research into brain tumours since the Committee's inquiry in 2016 you would like to draw the Committee's attention to?

A. In 2018 we published the NICE guidelines [vii]on the care and of patients with primary brain tumours and metastases. The TJ Centre initiative has I am glad to say recognised this in selecting the new Centres. It is important that all NHS Trusts and Commissioners are made clear as to their responsibilities to deliver these guidelines and to do this sustainably even as they wrestle with Covid issues. Delay at any point harms the patients and often their response to treatment. It is essential therefore that we recognise NOW that there are specific parts of the patient pathway that are currently at risk.

1. Access to GP assessment and referral for diagnostic imaging.
2. Delay in imaging procedures
3. Delay in reporting imaging to allow MDT review.
4. Delay in accessing review in OPD (video consultation not the best way to give difficult information)
5. Ensuring CNS support for patients
6. Reducing delay in admission for surgery for undiagnosed brain Tumour patients
7. Reducing the delay in access further oncological treatment eg radiotherapy
8. Reducing the delay in accessing surveillance imaging (see2 above)

B. A recent and growing phenomenon is the medical traveller with a Brain Tumour. I would estimate this as being about 200 patients currently. In the past this has been driven by such treatments as Proton Therapy – at the time not available in the UK. However now there is subtly different traffic that may be augmented by the impact of Brexit on drug regulation across the EC but not UK. There is increasing scientific evidence that the use of personalised vaccines to a patient's tumour may offer a safe and potentially useful adjunct to current mainline NICE approved therapy. Patients undergoing surgical decompression or biopsy of their tumour for formal pathology can submit (at a cost in Germany) their retained frozen tumour tissue for assessment of immunogenic surface antigens. From this companies (eg IOZK & CeGaT clinics in Cologne) can then produce a personalised vaccine for that patients tumour that can be regularly administered at a one of the nine or so clinics in Germany. Currently the technology is available in the UK. Also, the vaccines produced could be administerd in the UK. However, because this therapy is not based on a 'randomised trial' principle – -best result for the greatest number, NICE are not in a position to support this therapy. Importantly,

in this situation, vaccine production is not (because of absence of the need for scaling up) manufactured under GMP guidelines but only to a GLP standard. This prevents its use in the UK - despite the fact that any one vaccine is made and will only be used specifically in the one consenting patient is produced for, hence the risk is very low of problems. Currently UK regulations make this process untenable to the detriment of both further knowledge about immune treatments of brain tumours, but also for individual patients (who cannot afford the travel etc) to access this therapy. It is important to recognise that such is the increasing support for this type of therapy for GBM in Europe that the German centre have formed a nationwide program for delivery of this treatment to all German [viii]sufferers, and the therapy is lead by some of the most distinguished researchers in brain tumours in the EC. We need to think how we could include this 'personalised approach' stream in the current over stringent UK regulatory structure to allow specialists in the UK to offer these treatments where appropriate.

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[i] https://www.headsmart.org.uk/clinical/clinical-guideline/

[ii] Buszek, S.M., Al Feghali, K.A., Elhalawani, H. *et al.* Optimal Timing of Radiotherapy Following Gross Total or Subtotal Resection of Glioblastoma: A Real-World Assessment using the National Cancer Database. *Sci Rep* **10,** 4926 (2020). https://doi.org/10.1038/s41598-020-61701-z

[iii] https://www.nice.org.uk/guidance/ng12

[iv] https://www.ncri.org.uk/groups/brain-group/portfolio-maps/

[v] Aldape, K., Brindle, K.M., Chesler, L. *et al.* Challenges to curing primary brain tumours.*Nat Rev Clin Oncol* **16,** 509–520 (2019). https://doi.org/10.1038/s41571-019-0177-5

[vi] https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-oportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf (joint doc: DoH,NICE,NHRI,MHRA)

[vii] https://www.nice.org.uk/guidance/ng99

[viii] The Glioma Actively Personalized Vaccine Consortium (GAPVAC) approach is a highly personalized method being progressed through the GAPVAC-101 first-in-human clinical trial by a European Union-funded consortium, led by Immatics Biotechnologies GmbH (Tuebingen, Germany) and BioNTech AG (Mainz, Germany).

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Wednesday, 14 April 2021