OurBrainBank

Glioblastoma

The neglected disease in the cancer treatment revolution

A report on the state of care and therapies available to people diagnosed with GBM in the UK

July 2023

Glioblastoma: the deadly brain cancer that is being neglected in the treatment revolution

Why the current approach to GBM in the UK is failing and denies people living with the disease the same opportunities for personalised treatments as other cancer patients

Introduction

OurBrainBank (OBB) is a charity created by, for and with people living with the brain cancer glioblastoma (GBM) in the UK and US. OBB exists to support, inform and campaign on behalf of the growing community of people affected by GBM. This paper has been written from the perspective of people living with GBM and those supporting them. It describes the experience of that community in the UK and documents significant failures of the current treatment available.

The paper is intended for a general audience, to increase understanding and to stimulate public debate, as well as for the medical community, in order to contribute to the discussion about how to accelerate improvements in treatment options and in particular how to make personalised medicine available to all people living with GBM.

The paper begins with a description of GBM and the current approach to treatment for the general audience and then moves on to a more detailed discussion of the role of whole genome sequencing (WGS) in personalised treatment and the challenges to ensuring it is widely available.

Throughout this report these boxes contain quotes from OurBrainBank's interviews with people living with glioblastoma and their carers. These interviews were conducted remotely with participants recruited from a GBM Facebook group by web-video conferencing software in March and April 2023. The quotes have been viewed and approved for publication by the participants although their identities have been masked to protect their privacy.

Executive summary

Glioblastoma (GBM) is an aggressive form of brain cancer. It has a very poor prognosis. Despite being classified as a rare disease, it is the most common type of primary malignant brain tumour in adults.

Whereas significant progress has been made in recent years in the treatment of many

more common cancers, little progress has been made on GBM. The standard of care in the NHS has been unchanged for almost 20 years.

Spending on cancer research in the UK appears to correlate more closely with the total number of deaths than with lower percentage survival rates, leading to higher research spending on common cancers rather than those that are most lethal.

Advances in surgery for GBM have been made over the past two decades, but little has changed in terms of follow-up therapy, which remains based on radiotherapy with adjuvant chemotherapy.

Whereas many of the recent advances in oncology use personalised immunotherapies – treatments that stimulate the body's immune system to fight cancer cells – immunotherapy for GBM is only available within the NHS by accessing a clinical research trial.

In 2018 the government promised to make whole genome sequencing, used to identify mutational targets for personalised treatment, available to all patients with rare cancers, however in the last five years very little progress has been made on achieving this goal for brain tumour patients.

WGS requires frozen tissue samples for analysis, however there are extremely limited facilities for frozen tissue storage in the UK and whether tissue is frozen depends on variables not controllable by patients, including where they are being treated.

OurBrainBank (OBB), a charitable organization focused on improving the treatment options for people with GBM, believes that the disease is being neglected regarding research, treatment options and standard of care. The UK arm of OurBrainBank (OBBUK) argues that five vital steps should be taken immediately to improve the situation for GBM patients in the United Kingdom and to ensure they do not miss out on the benefits of the personalised cancer treatment revolution:

1. **Universal frozen tissue storage, with an attainable target for that being achieved to be set immediately;**
2. **Universal genomic sequencing for all GBM patients where tissue is available, with an attainable target for that being achieved to be set immediately;**
3. **Specific, reliable GBM information for patients and carers on NHS and other official UK government websites;**
4. **An increase in the number of UK drug trials for GBM, with a stretch target to be set immediately;**
5. **Translational research, that is, treatment-focused research that promises early transition from 'bench to bedside', to be given funding priority.**

OBB believes that these urgent steps will not only benefit people living with glioblastoma now and in the future, but also potentially the wider cancer community. In the words of OBB's founder, Jessica Morris, overcoming glioblastoma, one of the toughest cancers, may be the key to cracking them all.

1. What is glioblastoma?

Glioblastoma Multiforme, now usually called glioblastoma (GBM), is a cancer affecting the brain or spinal cord. It is a form of glioma, a malignant brain tumour comprised of glial brain cells that surround nerve endings in the brain. Glioblastoma can develop at any age but occurs more frequently in older adults.

Indicative symptoms often include headaches, nausea, vomiting and seizures, but the effects are variable and unpredictable, and depend on which part of the brain is affected. GBM may induce other symptoms such as paralysis, confusion, or loss of speech or memory.

My husband kept saying to me 'You need to help me... you need to find me something to keep me here as long as I can to see my daughter grow up.' And I couldn't do that.

Wife of man with GBM, NW England

GBM is classified by the World Health Organisation (WHO) as a high-grade (grade IV) cancer. Until 2021, grade III anaplastic astrocytomas were also referred to as glioblastoma. Though the reclassification aims to improve understanding of prognosis and optimal treatment for each subtype (Berger et al., 2022), it may mean that previously supported patients now have less support. (For that reason, OBB continues to include those impacted by grade III anaplastic astrocytomas within its work).

Both grade III and grade IV brain tumours are classified as high-grade because the cancerous cells tend to grow and spread more quickly than those of lower grade (grade I and II) cancers. This means a worse prognosis, and the need for swift and aggressive treatment. "Multiforme" in the name indicates that the tumours are heterogeneous or highly diverse, exhibiting many different mutations, making the cancer particularly difficult to treat.

GBM grows quickly. Median survival time from diagnosis to death, or median overall survival (MOS), (that is, the time from diagnosis until 50% of those affected have died), is around 14 months (Stupp et al., 2009). Only about 5% of people living with GBM survive more than 5 years (Stupp et al., 2017).

Rare diseases are classified by the UK government as those which affect fewer than 1 in 2,000 people (Department for Health, 2022). Annual worldwide cases of GBM are estimated at around 250,000 (Gliocure, 2017), which represents an incidence of between three and four per 100,000 (Ostrom et al., 2015). By comparison, breast cancer is the most frequent worldwide cancer, with 2.26m new cases diagnosed annually worldwide (WHO, 2020). In the UK, about 3,200 cases of GBM are diagnosed each year (Killworth, 2022). Despite its classification as a 'rare disease' it is the most common type of primary malignant brain tumour in adults (Ostrom et al., 2015).

Traditionally cancers have been categorised by the site of cancerous tissue in the body. Through research, improved treatments have emerged for many common forms of

cancer, increasing survival rates, though this has not happened with cancers of the brain (CRUK, 2022).

> ***If you have grade IV glioblastoma, you are literally just told to 'go away and have a walk in the park.' And that is what I remember my consultant saying to me 'just go away and just go and enjoy a walk in the park.' I came out of there and exploded 'A [expletive] walk in the park? I'm not a walk in the park guy, I want to live!'***
>
> **Man with GBM, N England**

A study of cancer research spending in the UK indicates that research fund allocation correlates more closely with the number of annual deaths rather than with lower survival rates. This may be related to heavy reliance on charitable grants to fund research. Charities focused on more common cancers attract more donations and volunteers because more people have been personally affected by them. Survival rates are higher in these cancers because of advancements flowing from research. Effectively there is a positive feedback loop for more common cancers which draws funding and research away from rarer cancers, and there is proportionally higher research spending on more common cancers, rather than those that are more lethal with a shorter MOS. For example, bowel cancer has a much higher survival rate than brain cancer, with more than 56% of diagnosed cases surviving more than 10 years, compared to 13.5% of all brain cancer cases (CRUK, 2021). However, bowel cancer research funding is much higher than the annual funding awarded to research into all brain cancers (see table 1).

Organ	Total UK deaths	Annual UK research spend	Surviving 1-year post-diagnosis	Surviving 10-years post-diagnosis
Bowel	16,807	£39.5m	75.5%	56.6%
Brain, other central nervous system (CNS) and intracranial	5,456	£17.6m	40.1%	13.5%

Table 1. *Comparative death rates, UK annual research spend and survival rates at 1- and 10-years post-diagnosis for bowel and brain cancers. Source: Cancer Research UK (2021)*

The figures in table 1 cover all brain cancers; Cancer Research UK (CRUK) does not publish data specifically related to GBM, but analysis of GBM survival rates estimate that only 0.71% of patients survive ten years post-diagnosis (Tykocki & Eltayeb, 2018). Five-year survival rate has been reported as between 4.1% (Stupp et al., 2005) and 6.8% (Siegel, Miller & Kemal, 2020). Comparing these rates with those in table 1 highlights that GBM is more lethal than other cancers of the brain and central nervous system.

Spending on research into all brain cancers lags behind other cancers. GBM is further

under-researched. GBM, along with other brain cancers, has been recognised as a cancer of unmet need by CRUK (2021).

In February 2023, the All-Party Parliamentary Group on Brain Tumours published a report called *Brain Tumours: Pathway to a Cure – breaking down the barriers* which revealed that of the £40 million committed by the government to brain tumour research in June 2018, as of 25th January 2023, just £15 million had been awarded. Further, £6 million of this was not easily identifiable as relevant to brain tumours[1].

Cancer type	NCRI spend (% of total research spend)	5-year survivability rate
Breast	£775m (7.8%)	85%
Leukemia	£551m (5.5%)	54%
Brain	£126m (1.3%)	12%

Table 2. *Spend by cancer site analysed by Brain Tumour Research. Source: APPG BT report (2023)*

The shortfall in spending of theoretically available funds on research into GBM indicates that there is a critical shortage of researchers, clinicians and studies focused on GBM. This at a time when the incidence of brain tumours is rising in the UK (UKCR, 2022). It is projected that annual cases of brain tumours will reach more than 14,000 by 2035 (UKCR, 2022). Though the focus of this paper is the UK, the global incidence of GBM also appears to be rising (Grech, et al., 2020). The causes of this are undetermined.

2. Current treatment options

NHS standard of care

Treatment in the NHS follows what is known as the Stupp protocol, named after Roger Stupp, the lead author of an influential 2005 study of GBM[2]. ***OBBUK has evidence that this is often presented to patients as 'the gold standard' of treatment. We believe that, while this may have been true at the time the study was published, it is a misrepresentation to state that the Stupp protocol remains the 'gold standard' today.***

The Stupp protocol advocates neurosurgery with maximal resection, that is, removing as much of the tumour tissue as possible, followed by a course of radiography and adjuvant chemotherapy, usually 6-12 weeks of Temozolomide. For most GBM patients within the NHS this is the only available treatment. A few patients being treated at research centres may be offered places on drug trials, but these are extremely limited. In addition the criteria for trial eligibility are often restrictive and the consent process can be daunting

1 *https://www.braintumourresearch.org/docs/default-source/default-document-library/appgbt/btr_2667_appgbt-briefing_pathway_a4_36pp_2023_singles_lores.pdf?sfvrsn=27ac8501_3*
2 *https://www.nejm.org/doi/full/10.1056/nejmoa043330*

and intimidating for patients and their carers who may only just be beginning to understand the impact of a GBM diagnosis.

> ***There was just no support from the neuro-oncologists to discuss anything outside the NHS protocol. Don't get me wrong. I think the NHS is fantastic in its own way. The people that work for them are amazing, But we have just got that one thing. There is no deviation from it, unless you live down south somewhere. If you're, say, in London, they will discuss further options.***
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> **Man with GBM, Central England**

The National Institute for Health and Care Excellence (NICE) approves NHS funding for treatments in England, Wales and Northern Ireland based on evaluation of evidence from relevant studies and a stringent cost-benefit analysis. (In Scotland the Scottish Medicines Consortium (SMC) provides equivalent advice on the clinical and cost-effectiveness of all new medicines). Currently NICE guidelines for grade IV Glioma (Glioblastoma) restrict approved treatment to the Stupp Protocol. The guidelines for approved treatment date back 18 years, to shortly after the publication of Stupp's 2005 paper.

The guidelines for NICE approved treatment of GBM are shown as appendix 3[3].

Advances in surgery

In the last two decades there have been important advances in surgery for GBM. There has been an increasing use of 'awake craniotomy', during which the patient remains awake whilst their brain activity is continuously monitored to improve the chance of removing as much of the malignant tissue as possible without causing damage to brain function (Moiraghi et al., 2021). However, such is the delicacy of the craniotomy procedure that even the most skilled neurosurgeon is highly unlikely to be able to remove all the cancerous tissue, and inevitably some tumour cells remain, which become the site of regrowth of the tumour, and thus the likelihood of recurrence is extremely high.

> ***We're a reasonably well-educated couple. We did endless research. People have been really generous. Our family was very generous, but I would say lots of people wouldn't have the wherewithal to deal with all that we did, and that's the honest answer.***
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> **Mother of child with GBM, SE England**

Administering 5-Aminolevulinic Acid (5-ALA), also known as the 'pink drink', prior to surgery has increased the chances of maximal resection. 5-ALA causes tumour cells to glow under ultraviolet light and assists in identifying malignant tissue that must be removed. This is of great value when the surgeon is working at the delicate margin of the tumour and healthy tissue (Baig Mirza et al., 2021). Following a successful campaign by the Tessa Jowell Brain Cancer Mission (TJBCM) the pink drink has been available to UK high-grade glioma patients since May 2018, when the UK government committed to a national rollout of 5-ALA (Brain Tumour Charity, 2022).

3 *https://www.nice.org.uk/guidance/ng99*

Options outside the NHS

Although most people diagnosed with GBM in the UK are treated within the NHS, a small number contract doctors on a private basis, including neuropathologists and oncologists abroad, to access treatments not currently approved for use by NICE and therefore not offered by the NHS. The costs of such treatments can run into hundreds of thousands of pounds and therefore they are only available to those who have the financial means or those who are able to raise money through crowdfunding or other sources.

Optune

One such treatment is Optune, developed by the Novocure company[4]. Optune is an electrical device which is worn on the head and applies electro-magnetic fields, called 'tumour treating fields' (TTF) to the brain, designed to impede the division, and thus growth of cancer cells.

Trial results suggest that Optune use may be associated with a longer survival period than treatment using chemotherapy alone (Stupp et al., 2017). In the study, two groups were observed, one receiving chemotherapy alone, and the other with the addition of an Optune device worn for at least 18 hours per day. Median progression-free survival of 6.7 months was observed in the Optune group. This compared to 4.0 months in the group receiving only chemotherapy. However, there is some controversy within medical academia regarding this trial including questions about aspects of its methodology.

The hardest thing is when your son is diagnosed with a brain tumour, and the second hardest thing is where you have to suddenly become a research scientist yourself. And find out all the stuff that there is to find out and all the other treatments.

Father of child with GBM, S England

Optune was approved for use by GBM patients in the United States by the Federal Drug Agency (FDA), (the US equivalent of NICE), in 2011. NICE started an appraisal of Optune in 2018/19, but that process was suspended in 2020. NICE said Novocure had not been able to source the evidence necessary for their consideration within the timescale of the appraisal. Therefore, currently, NICE has not approved Optune as an NHS-funded treatment for UK GBM patients. Optune can be accessed in the UK, but only through a private prescription. The cost of the device is about £20,000 per month, which currently will not be covered by UK private health insurance.

3. Immunotherapy

Many of the most promising recent treatments for a wide range of cancers involve immunotherapy. Immunotherapies are treatments that stimulate the body's immune system to fight illnesses and invasive cancer cells. Immunotherapies may be employed alone, or in conjunction with other treatments.

4 *https://www.optune.com/clinical-study-results*

Clinical trials have demonstrated successful immunotherapeutic treatments for a range of cancers including those of the skin, lung, breast, liver, colon, and kidney (Zhang & Zhang, 2020). Over the last two decades immunotherapy drugs have been approved by regulators in the United States and the UK to treat many types of cancer.

Immunotherapies and brain cancers

Immunotherapy trials for cancers of the brain and central nervous system (CNS) have been limited and in the studies that have taken place there have been very few promising results for brain cancers, and fewer still for GBM patients (Yu & Quail, 2021; Habashy et al., 2022). There are several factors that contribute to this.

Brain as 'Black Box'

In conversations with their patients clinicians will often refer to the brain as a 'black box,' protected from the rest of the patient's body and the outside world by the 'blood-brain barrier' (BBB). The BBB is a network of closely spaced cells that restrict potentially harmful substances from passing through. This limits the immunotherapy drugs that can be administered to the brain to those composed of molecules small enough to pass through the barrier.

Tumour heterogeneity

GBM is one of the most heterogeneous cancers. In an individual case of GBM there are likely to be multiple mutations involved in the tumour's growth; any one case of GBM is very unlikely to have a similar mutational profile to another. This creates several challenges: a) the need for detailed pathological analysis to identify potential mutational targets for personalised treatments; b) the fact that there cannot be one standardised drug treatment that is appropriate for all GBM patients, but rather a whole arsenal of therapies is needed to target the many different mutations behind the disease.

Importance of genomic profiling

The heterogeneity of GBM means that in order to select immunotherapy drugs that stimulate a response from the body to attack and restrict the growth of the tumour, it is important to identify the genetic mutations in the brain cells that are involved in tumour growth. This can only be adequately achieved through genetic profiling and the use of genomic sequencing.

The UK has advanced genomic sequencing facilities and is an important global centre for genomics. The UK government has also promoted the expansion of genomic profiling to improve treatment for patients who have genetically determined diseases.

In October 2018, then Health and Social Care Secretary for England Matt Hancock announced the ambition to map five million genomes within five years for 'faster diagnosis and personalised care' of those with rare diseases. The government also committed to offering adults with hard-to-treat cancers whole genome sequencing from 2019. However, research by OBBUK, based on freedom of information (FOI) requests and discussions with people living with GBM, indicates that very few have been offered any form of genomic

sequencing in their NHS treatment.

When approached by OBBUK in December 2022, the government's Department of Health and Social Care (DHSC) confirmed that the department holds no information about the total number of patients who have had their whole genome sequenced. The exact wording of the FOI request and the DHSC response are presented in appendix 1.

> ***It was one constant battle of trying to navigate what was right for him. We had a genomic analysis done but I think it was far too late. The analyst had a conversation with me and my husband and said one of the markers, or whatever they call them, had duplicated more than they had ever seen in any other glioblastoma patient. It was like his were just so out of control. It was just crazy. He recommended all these different cocktails but half of them weren't available here. And if we lived in America, we could have got them.***
>
> **Wife of man with GBM, SW England**

Further FOI requests in January 2023 revealed that of the four devolved health services, only NHS England held data. (NHS England's FOI response is in appendix 2.) At that time, it was reported that a total of 61 patients with either diagnosed or suspected GBM had received whole genome sequencing through the NHS England genetic medicine service. A total of 291 patients with suspected or diagnosed brain tumours had received WGS. The same data release revealed that genomic testing in England began in April 2021 and that 556,000 molecular diagnostic tests for cancer had been performed from that date to December 2022.

A total of 24,875 of these tests involved WGS, 291 of which were carried out for brain tumour patients, and 61 of these were for GBM patients. This means that only 1.2% of the tests were for brain tumour patients and an even smaller percentage, 0.2%, were for GBM patients.

With about 10,300 brain tumour diagnoses, and about 2,700 GBM diagnoses in England each year, OBBUK estimates that up to the end of 2022 whole genome sequencing analysis was only carried out on approximately 1.6% of brain tumour patients and 1.3% of GBM patients diagnosed since April 2021.

The proportions are even smaller when the number of whole genome sequencing tests is expressed as a percentage of patients diagnosed since January 2019, the date when the government said tests should have been available: for brain tumour patients the figure is 0.7% and for GBM patients it is 0.57%. (For calculations and assumptions see Appendix 3).

These data confirm that GBM, and indeed all brain tumours, have been severely neglected in the programme announced in 2018. These figures are for England. The amount of testing carried out in Scotland, Wales and Northern Ireland is believed to be substantially less than in England.

As of January 2023, the DHSC's ambition to map five million full genomes by 2023 was just over 10% complete, with 80% of the timescale elapsed.

OBBUK has made further FOI requests asking for any available data for 2023, but so far has received no reply; however, from conversations with several prominent clinicians working in the field it appears there has been a welcome increase in WGS of GBM patients in the first half of 2023, which may have increased the percentage figures by a point or two but is still a very long way short of the 2018 target.

Impediments to research and drug development for GBM

GBM is not well understood in part due to historically low investment in basic neuro-oncology. This means that the therapeutic vulnerabilities of the disease are not well known and cannot be tested. Moreover, research efforts are hampered by a lack of national resources in tissue banking and model development. This slows progress and reduces the impact of research.

Some other aspects of GBM make it less attractive than other cancers to the pharmacological companies for research and development: a) the relatively small number of patients undergoing treatment at any one time; b) the heterogeneity of the tumours involved; and c) the fact that emerging treatments appear, at best, to prolong life for short periods (~3 months), all mean that the opportunity for pharmaceutical companies to recoup their substantial development costs on drugs produced for the GBM community is significantly less than developing drugs for other more common cancers.

OBBUK believes that the factors outlined above should not be a brake on the development of immunotherapeutic treatments for GBM. Not only does this deny people living with GBM the chance of extended survival periods and better quality of life, but ultimately the approach is short-sighted. In the words of OBB's late founder, Jessica Morris, if the medical community can make significant advances in the treatment of GBM, one of the most difficult cancers to beat, then those advances are highly likely to provide significant benefits in the treatment of other cancers.

Immunotherapy for GBM

Notwithstanding the impediments to research on immunotherapy for GBM, to date several have been explored. However, so far, few have produced promising results in phase III trials or beyond. A 2022 review classifies them in the following five groups:

- checkpoint inhibitors
- chimeric antigen receptor (CAR) T-Cell therapy
- vaccine-based therapies
- viral therapies
- cytokine-based approaches.

(For a full summary see: Sener, Ruff, and Campian, 2022).

Vaccine therapies

At present, some of the most promising results have come from vaccine trials, in particular, dendritic cell vaccinations. Vaccine-based therapies are designed to elicit anti-tumour

responses, by priming T-cells with immunogenic antigens unique to tumour cells or antigens detected at elevated levels on tumour cells (Wen et al., 2020).

(DCVax-L) Autologous tumour lysate-loaded dendritic cell vaccination

A recently published study into the personalised vaccine DCVax-L has attracted attention. The vaccine is produced from the patient's own dendritic cells. Cells are removed from blood and the tumour site, immune cells are then separated from blood, and exposed to tumour cells to 'teach' the extracted cells the difference between malignant cells and healthy ones. These 'educated' cells are reinjected into the patient, where they in turn teach other immune cells to identify and attack malignant cells in the patient's body.

We did loads and loads and loads of research and the thing that we were interested in is DC Vax. But we knew the cost was hugely prohibitive. I kept haranguing his consultant about DCVax. Basically, his consultant said to us, 'you know he's got 12 to 18 months to live,'... 'Don't drag him round the world trying to find a treatment, just live your life and do the best you can.'

Mother of child with GBM, S England

Recent trial results have offered hope that DCVax-L can prolong life of GBM patients when compared to treatment with chemotherapy alone (Liau et al., 2022). However, there is a dispute within the medical community regarding these findings, given the study's design, and the methods used for analysis (Preusser & van den Bent, 2022).

NICE started an assessment of the vaccine for newly diagnosed GBM patients, at the Department of Health's request, in early 2017. However, that assessment was suspended in late 2018 when Northwest Biotherapeutics, the company developing DCVax-L, did not provide data requested by NICE. Since the publication of the 2022 paper the NICE appraisal status has changed from 'suspended' to 'in progress'. There are no published expected timelines for updates.

OBB has contacted NICE to request further information about expected timescales. An email response dated 17th January 2023, indicates that NICE are in regular contact with Northwest Biotherapeutics and expect to progress the evaluation of DCVax-L in early 2023. According to NICE the standard timescale for an evaluation process is about 40 weeks (NICE, 2023)[5].

Other vaccines

Several other trials have explored vaccine interventions. Only two (in addition to DCVax-L) have reached phase III clinical trial stage. Rindopepimut is a peptide vaccine that targets the epidermal growth factor receptor variant 3 (EGFRvIII). The phase III clinical trial stage was ended in 2018 when trial results indicated no increase in mean overall survival.

Phase III results for another vaccine, Wilm's Tumour 1 (WT1) peptide vaccine, are expected in late 2023 (Sener et al., 2022).

5 *https://www.nice.org.uk/guidance/indevelopment/gid-ta10143*

The future of immunotherapies for GBM

Other current GBM immunotherapy trials, some of which have shown promising results, are still at small-scale trial stage and are years from being available to people living with the disease. However, the advances that have been made for other cancers suggest that immunotherapy, targeting specific mutations, offers the best hope of effective treatment for GBM and should be pursued with urgency.

There is research currently being conducted with GBM patients in the UK, notably a study at Cambridge Addenbrookes hospital. The study is a three-year examination of GBM patients, which aims to map tumour and 'healthy' tissue in 255 patients to examine patterns in genomic data to inform improved treatments[6]. (See section 5 below).

The heterogeneity of GBM, whereby different GBM patients are likely to have widely different mutations associated with or driving their tumour growth, means that universal genomic sequencing is imperative to achieve the goal of offering all patients treatments that target the relevant mutations involved in their disease - the approach known as 'personalised medicine'. The current standard treatment is neither personalised, nor targeted.

4. Tissue storage

Genomic sequencing is not possible without appropriate tissue (and/or blood samples) to sequence. Cancerous brain tissue is routinely preserved after craniotomies for standard pathological purposes, such as determining wild type and methylation status, the results of which help plan standard treatment. However, the method of storage, which determines whether genomic sequencing can be carried out, is not uniform across the country.

There are two principal methods of storing and preparing tissue for histological analysis: formalin-fixed paraffin-embedded (FFPE) blocks, and preserving samples through freezing.

FFPE blocks have been used for many years and the technique is cheaper than frozen tissue storage. In FFPE samples proteins are preserved, but they are also denatured, meaning that they are not biologically active. This limits their value for many types of study including immunohistochemistry (IHC), where different antibodies can indicate healthy or diseased tissues. Moreover, the nucleic acids, DNA and RNA, are preserved poorly in FFPE tissue, severely limiting its use for genetic analyses.

It's gone. The sample is in the bin! I'm sure the average cost of keeping the tissue in the freezer is not peanuts, but it doesn't feel like an invalid use of resources. For research potential, for future treatments... Let's do the sequencing now... But of course it's pay to play isn't it? Why is our oncologist not doing that? Maybe he hasn't got time or it's because he thinks it's pointless, but it's not providing good patient centred care, is it?

Woman whose partner had GBM, SW England

6 *https://www.cuh.nhs.uk/news/landmark-nhs-testing-and-treatment-for-brain-cancer/*

When tissue is frozen it is encased in liquid nitrogen and stored in an ultra-cold freezer at lower than minus 80 degrees Celsius. This preserves proteins in a 'native state', making IHC analysis and biochemical analysis possible. As tissue degrades very quickly at temperatures above minus 80C, there are associated maintenance and infrastructural costs. Moreover, training is required for technicians to understand the techniques to ensure tissue is frozen as quickly as possible and then remains frozen. This requires access to liquid nitrogen and an ultra-cold freezer at the point of resection. Frozen tissue remains biologically active, preserving DNA, RNA, and native proteins. Frozen tissue samples are the only ones that can be sequenced fully to successfully identify potential mutational targets for immunotherapies and other personalised treatments.

There are far fewer frozen tissue storage facilities in the UK than hospitals carrying out craniotomies for GBM. Therefore, patients operated on at hospitals without frozen storage on-site or nearby are at a heavy disadvantage compared to patients at larger facilities where frozen storage is available.

OBBUK believes that the NHS should move as rapidly as possible towards ensuring all resected tissue is preserved in a frozen state, so that genomic sequencing can be carried out for every GBM patient, thus removing what is, in effect, a postcode lottery.

The preservation of resected tissue is also of great importance to the research community. Even in cases where the bulk of resected tissue is preserved in frozen form, it is usual for some of the tissue, especially that which is vacuumed from the tumour margin, to be disposed of rather than preserved. Preservation of all tissue would make a significant and vital resource available to the research community.

Associated costs

OBB has looked at the costs of providing universal frozen tissue storage. The calculations have been made from data extracted from secondary sources and are limited as a result. Therefore, it is difficult to provide accurate cost estimates for the measures proposed in 'the way forward' section of this paper. The calculation assumes that no staff or infrastructure currently exist and extrapolates new costs on that basis. Actual spending is likely to be less than the figures calculated here, as some of the staffing and infrastructure already exists within NHS neuro-oncology centres.

For these calculations the assessment of infrastructure requirements includes one-off and maintenance cost estimates. It has been suggested that skilled pathologists are vital for brain tissue biobanking (Bevilacqua et al., 2010). Thus, the costing includes the salary of one pathologist but not the cost of training or recruiting pathologists – it assumes a supply of skilled healthcare staff. Web searches of 'neuro-oncology research nurse' and 'clinical pathologist' show starting salaries of between £27,055 and £34,012[7].

To retain the quality of DNA and proteins in brain tumour tissue, ultra-low temperature (ULT) storage is required. (Shabihkhani et al., 2014). The procurement cost of ULT

7 *https://www.healthcareers.nhs.uk/explore-roles/doctors/roles-doctors/pathology/chemical-pathology*

freezers varies based on capacity, but retail costs range from c. £11,000 to c. £17,000[8]. For consistency, ~740 litre capacity models are assessed for maintenance costs. A ULT freezer uses ~15.1 kWh per day (Shabihkhani et al., 2014) which can be calculated as a daily cost of £5.13 assuming 34p/kWh; this is the national average price in the UK, October 2022[9]. It has been confirmed anecdotally by staff in UK-based biological tissue banks that a ULT freezer of this size can hold between 2,000 and 6,000 frozen tumour samples, depending on the amount of tissue resected. Given that there are ~3,200 new annual cases of GBM in the UK, this means that a very small number of ULT freezers would be required to meet demand.

There are seven regional hubs for WGS in the UK[10]. This is used as a basis for required site numbers – full estimates are detailed in table 3.

	Cost per staff member (£)	Cost per ULT (£)	Annual energy cost (£)	Total cost UK wide (£)
Range	27,055 - 34,012	11,772.34 - 17,492.02	1872.45	273,663.83 - 373,635.29
Maximum	34,012	17,492.02	1872.45	373,635.29

Table 3. *Projected costs associated with adoption of UK-wide universal tumour tissue freezing. Final total costs are calculated based on the existing model of 7 regional genomic testing hubs.*

5.Two approaches to increasing WGS for brain cancer: improving testing and reporting pathways

There are multiple reasons why the 2018 commitment to providing WGS to everyone diagnosed with glioblastoma has not been achieved, including:

- A nationwide shortage of medical oncologists with training in and understanding of molecular oncology means that many patients will be in the care of clinicians who are not comfortable with or knowledgeable about the latest developments in precision medicine.
- Many patients will receive their initial treatment in centres that do not have the facilities to handle and preserve frozen tissue, and therefore the opportunity to perform sequencing is lost from the outset.
- Even when suitable tissue is obtained, currently the pathways/ pipelines for handling it in terms of analysis and reporting are often not well established or efficient. Batch processing of tissue means that there can be considerable delays before a sample is sequenced. OBBUK has heard of cases where it has taken more than 400 days for the

8 *https://www.fishersci.co.uk/gb/en/browse/90106033/ultra-low-temperature-freezers*
9 *https://energysavingtrust.org.uk/about-us/our-data/*
10 *https://www.england.nhs.uk/genomics/genomic-laboratory-hubs/*

results to be analyzed and reported. Clearly in the case of a disease with an MOS of around 14 months this is completely unacceptable.

Currently two different projects in England are trying to find ways to improve the efficiency of the WGS analysis and reporting pipeline.

Minderoo Precision Brain Tumour Programme

The aim of the Minderoo Precision Brain Tumour Programme, at Addenbrookes Hospital in partnership with the Minderoo Foundation, University of Cambridge, the NHS, and the sequencing company, Illumina, under its lead Mr Richard Mair, is to identify the feasibility and utility of whole genome sequencing for glioma.

The programme is exploring the most effective way to use genomic information to better diagnose and plan targeted treatment in glioma. The programme aims to successfully integrate genomic information about a person's tumour, which can be used to diagnose and plan targeted treatment, into routine care. A new platform trial, which has recently been funded, will improve access to precision therapy, whilst also reducing the time from drug to patient and providing novel methods for biomarker ratification and treatment group identification.

By identifying and testing pathways at the local level it is hoped that the study could be used as an exemplar, facilitating adoption of the approach nationally, across the NHS. The project argues that by demonstrating feasibility, and through the identification of patient benefit, it will set a new benchmark for treatment, which can act as a precision medicine template for brain cancer patients across the country.

Brain Matrix

The Tessa Jowell BRAIN MATRIX study is working with the Tessa Jowell Brain Cancer Mission Equity of Access for Genomic Testing task force to develop a strategy to improve patient access to genomic testing on the NHS. As highlighted in this paper, the current situation is of wide variation, from no access to WGS to some access through the NHS. Led by Professor Colin Watts, Chair of the University of Birmingham Brain Cancer Programme, the project is seeking ways to support the operational infrastructure to ensure the processing of the delivery of patient DNA for sequencing. It is also looking at how to support the reporting and analysis pipeline of the data generated so that patients can benefit as quickly as possible.

The project has proposed setting up a Genomic Tumour Advisory Board (GTAB) specifically for brain cancer patients, with a coordinator to ensure tissue delivery to the sequencing company, Illumina. It will also set up a Genomic Laboratory Hub to facilitate reporting of the results by investing in a dedicated clinical scientist. A pilot scheme is being established with a view to expanding it across the UK as genomic testing evolves and becomes more routine.

Further, the aim is that the development of the testing and reporting pathway will be supported by both Genomics England (GEL) and NHSE, and beyond that will ensure equity

of access for patients in the devolved nations.

Once established, the brain cancer GTAB would support the learning and training of the next generation of neuro-oncologists, pathologists, and clinical scientists. It would also support engagement with pharma and industry to improve access to new drugs and the latest testing technologies.

6. The way forward

OBB's mission is to move GBM from terminal to treatable. Having surveyed the current situation for people living with GBM, OBBUK believes there are five critical steps that should be taken immediately to improve the situation for GBM patients and to ensure they do not continue to be neglected in the cancer treatment revolution that is positively impacting other cancers:

1. Universal frozen tissue storage, with an attainable target for that being achieved to be set immediately.
2. Universal genomic sequencing for all GBM patients where tissue is available, with an attainable target for that being achieved to be set immediately.
3. Specific, reliable GBM information for patients and carers on NHS and other official UK government websites.
4. An increase in the number of UK drug trials for GBM, with a stretch target to be set immediately.
5. Translational research, that is, treatment-focused research that promises early transition from 'bench to bedside', to be given funding priority.

1. Universal frozen tissue storage

For individual patients, the possibility of benefiting from innovative personalised treatments depends on genomic sequencing. This is not currently available to all patients. For the government to fulfil its 2018 promise of offering sequencing to all patients with rare diseases there needs to be an urgent roll-out of frozen tissue storage facilities across the country so that no one is at a geographical disadvantage.

The GBM research community also relies on the availability of well-preserved tumour tissue. Establishing universal frozen tissue storage will ensure the best possible resource for this community.

OBBUK believes that failing to freeze resected tumour tissue is a preventable limiting factor to many patients' quality of medical care, quality of life, and overall survival.

2. Universal genomic sequencing for all GBM patients where tissue is available

Brain and CNS cancers are recognised as diseases of unmet need and within this category GBM is a further understudied disease. Universal frozen tissue storage should provide several positive changes for individual patients, future patients, researchers, and clinicians.

- For the individual patient, WGS may inform clinicians of potential targets for personalised medicine.
- For the wider patient group and researchers, more genomic sequencing may identify patterns and commonly observed targets, crucial for developing effective treatments.
- For clinicians, more detailed information about tumour composition and improved access to targeted treatments will allow matching of treatments to patients for greatest effectiveness.

Theoretically greater genomic sequencing may also have benefits beyond GBM. Gaining insights from genomic sequencing in GBM patients may lead to applications in other brain tumours and cancers beyond the brain area. To paraphrase OBB founder Jessica Morris, GBM is the most difficult cancer to understand, thus, insights into GBM are likely to have applications elsewhere. In developing effective treatments for GBM we may well be able to apply the new findings to cancer knowledge as a whole, thus improving treatment beyond GBM.

3. Increase the number of trials for GBM

GBM suffers from inadequate levels of research including a failure to allocate available funds to dedicated research projects.

OBBUK believes that more trials are needed to investigate the development pathways of GBM and potentially beneficial treatments. Further research is required to understand the unique challenges that GBM presents.

The cost-benefit arguments that push research in the direction of more common cancers fail to take into account that improvements in the understanding and treatment of GBM are likely to benefit many more than just GBM patients. Making real progress in the treatment of one of the most aggressive and hard-to-treat cancers may lead to real progress in the treatment of many other, more common cancers.

4. Better GBM information on NHS and other official websites

A GBM diagnosis is devastating for patients and their families. This is exacerbated by the pace at which decisions for treatment need to be made. GBM is classified as a rare disease, and for many the first time they hear the term is when informed of the diagnosis. OBBUK has frequently been told of patients and their loved ones being told not to Google GBM. Yet, when they try to find out more, they almost always have to resort to multiple, and sometimes, unverified sources.

One contributory factor is the lack of information about GBM on official NHS websites. www.nhs.uk delineates between 'malignant brain tumour (brain cancer)' and 'benign brain tumour (non-cancerous)'. On the brain cancer page, GBM is not mentioned; only basic information is provided about tumour grading, treatment, and outlook, with signposting to other organisations such as The Brain Tumour Charity, Brain Tumour Research, Cancer

Research UK, and Macmillan Cancer Support. These organisations are reputable, and provide much accurate and helpful information, however ***OBBUK feels the absence of GBM from the NHS website is indicative of the neglect people living with GBM have suffered. OBBUK believes that GBM should be given equal prominence with other cancers and should have a dedicated NHS page providing reliable information.***

5. Increased urgency in moving research innovations from bench to bedside

As further research and trials are conducted OBBUK calls for these to be designed to facilitate the rapid roll-out of treatments that can be translated from what is termed 'bench to bedside'. With currently very few treatment options available, GBM patients should benefit from the earliest introduction of those that show promise. This implies that a) NICE should be as flexible as possible, within their existing guidelines, to allow early adoption; and that b) the guidelines should be under regular review to ensure that they are appropriate for assessing promising treatment for rare diseases even where there may be limited trial evidence.

OurBrainBank

We're a patient led movement dedicated to moving glioblastoma (GBM) from terminal to treatable. We're on a mission to support, inform and empower every person who has GBM.

We focus on GBM – one of the most complex and aggressive brain cancers – because, in the words of our founder, Jessica Morris, overcoming one of the toughest cancers may be the key to cracking them all.

Appendices

Appendix 1: FOI request sent to Department of Health and Social Care and each nation's NHS.

In 2018, then Health and Social Care Secretary Matt Hancock, announced the 'ambition to map 5 million genomes': https://www.gov.uk/government/news/matt-hancock-announces-ambition-to-map-5-million-genomes

In this ambition, it was stated that:
'From 2019, all seriously ill children will be offered whole genome sequencing as part of their care.'

AND

'Adults with certain rare diseases or hard-to-treat cancers will also be offered the same option from 2019.'

There are four questions I have based on these statements.

1. What is the total number of patients to have been successfully mapped?
2. What is the total number of patients mapped because of glioblastoma multiforme (GBM) diagnosis?
3. What is the total number of patients mapped as a result of a brain tumour?
4. What is the total number of adults mapped?

I appreciate your answers in this matter. If you need clarifications, I can be contacted on the methods detailed below.

Title: **Mr**
First Name: **Christopher**
Last Name: **Panks**

Appendix 2: FOI request (Ref: 2301-1907179) NHSE: 0338262

NHS England holds information in relation to your request. Please note, however, that the figures below capture the latest information available that is held by NHS England. Work is ongoing to introduce patient-level contract monitoring in the NHS Genomic Laboratory Hubs to capture activity, technology and access information which will inform the development and embedding of a sustainable commissioning model. Therefore, the figures below could be an underrepresentation of actual activity.

What is the total number of patients in England to have been successfully mapped?
Since April 2021, over 556,000 cancer molecular diagnostic tests have been performed, including over 84,000 next-generation sequencing cancer panels.

What is the total number of adults mapped in England?
Up to December 2022: 432,171 adult patients have received a genomic test through the NHS

GMS. 24,875 adult patients have been referred for a whole genome sequence through the NHS GMS as a patient or the relative of a tested patient.

What is the total number of patients in England mapped because of glioblastoma multiforme (GBM) diagnosis?

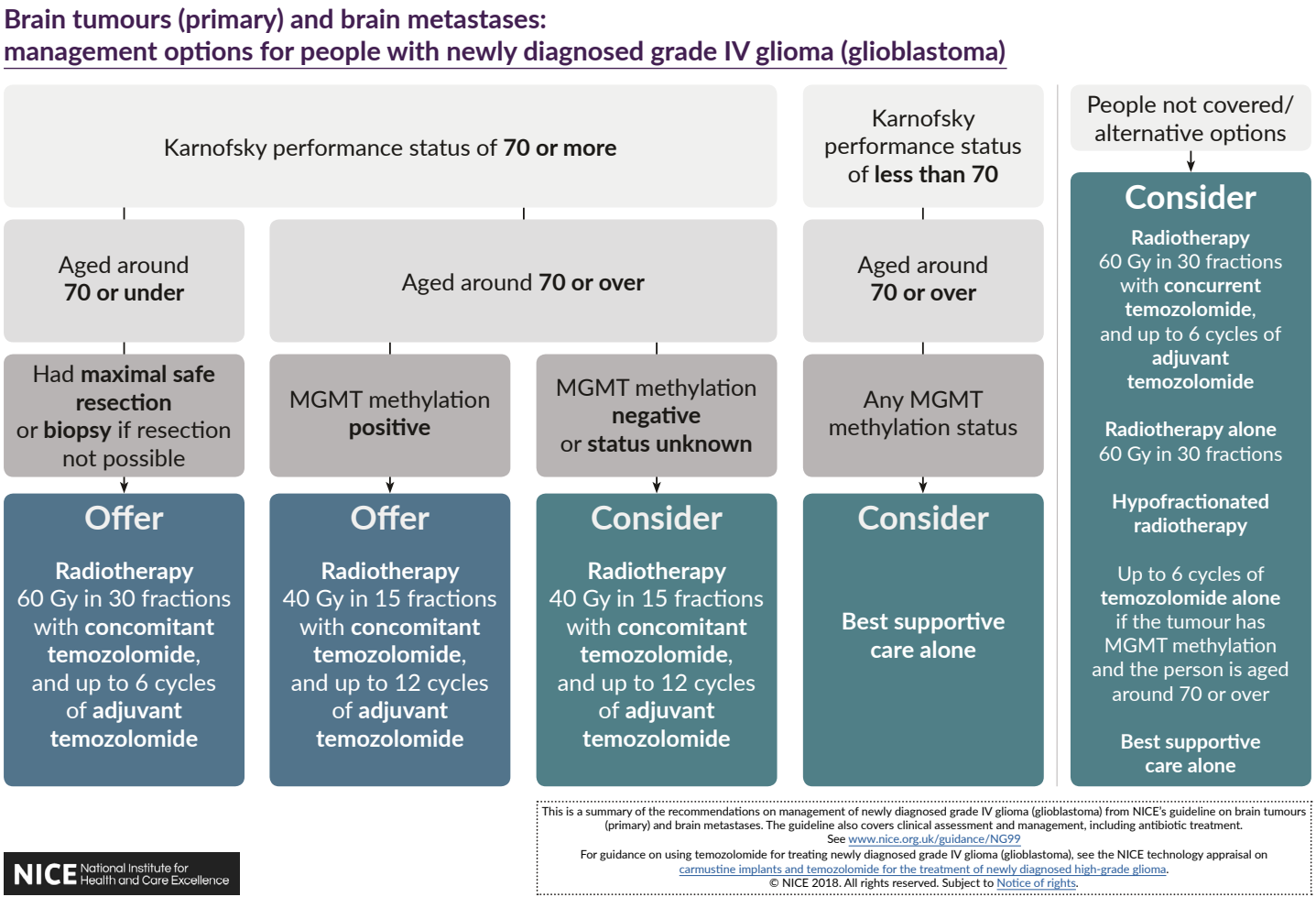
61 GBM cases have gone through the NHS GMS pipeline for whole genome sequencing to date.

This figure includes both suspected and diagnosed GBM cases. Patients may also receive next-generation sequencing panel testing for this indication, and in total for all clinical indications over 84,000 of these tests have been performed since April 2021.

What is the total number of patients in England mapped because of a diagnosed or suspected brain tumour?

291 cases as a result of a diagnosed or suspected brain tumour have gone through the NHS GMS pipeline for whole genome sequencing to date. Patients may also receive next-generation sequencing panel testing for this indication, and in total for all clinical indications over 84,000 of these tests have been performed since April 2021.

Appendix 3



NICE visual guidelines for treatment of Glioblastoma. (NICE, 2022)

The diagram shows the differences in treatment doses of radio and chemotherapy based on age and Karnofsky performance status (PS) scores. The Karnofsky scale is used to assess a patient's functional impairment with scores from 0-100, with higher figures indicating greater daily functioning.

Appendix 4: Calculations based on FOI data

UK nation	2021 populations	Percentage of UK population	Source
England	56,490,048	84.3%	Office for National Statistics
Scotland	5,479,900	8.2%	National Records of Scotland
Wales	3,107,494	4.6%	Office for National Statistics
Northern Ireland	1,903,175	2.8%	Northern Ireland Statistics and Research Agency
Total	66,980,617		

UK nation	Annual glioblastoma (GBM) cases
England	2,698 (approx)
Scotland	262 (approx)
Wales	147 (approx)
Northern Ireland	90 (approx)
Total	3,200

Source: Kilworth

UK nation	Annual brain tumour (BT) cases
England	10,359 (approx)
Scotland	1,008 (approx)
Wales	565 (approx)
Northern Ireland	344 (approx)
Total	12,288

Source: Cancer Research UK

NHS England whole genome sequencing figures (WGS) April 2021 – December 2022 (21 months)		
All WGS	24,875	
BT WGS	291	1.2%
GBM WGS	61	0.2%

Source: NHS England

GBM diagnoses over 21 months - England	4,721
BT diagnoses over 21 months - England	18,128

Therefore:

NHS England 21 month WGS success rate	
GBM	1.29%
BT	1.61%

GBM diagnoses over 48 months - England	10,790
BT diagnoses over 48 months - England	41,435

Therefore:

NHS England 48 month WGS success rate	
GBM	0.57%
BT	0.70%

Authors of this report

Christopher Panks, Researcher, OurBrainBank UK

Richard Clemmow, Trustee, OurBrainBank

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The views and proposals expressed in this report are those of the board of trustees of OurBrainBank (UK). They do not necessarily represent the views of any advisors or contributors.

UK Trustees

OurBrainBank

OurBrainBank is a charity created by, for and with people living with glioblastoma. It works in the United Kingdom and the United States. OBB assists people living with glioblastoma by the provision of support, assistance and information and campaigns for research into the nature, causes, diagnosis and treatment of glioblastoma. OBB seeks to make global connections to inform, support and expand our ever-growing community of people affected by glioblastoma.

OurBrainBank.org

Contact: **ukinfo@ourbrainbank.org**

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