



Mind Over Matter: Confronting Challenges in Post-Mortem Brain Biobanking for Glioblastoma Multiforme

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ABSTRACT: Over the past 10 years, there has been limited progress for the treatment of brain cancer and outcomes for patients are not much improved. For brain cancer researchers, a major obstacle to biomarker driven research is limited access to brain cancer tissue for research purposes. The Mark Hughes Foundation Brain Biobank is one of the first post-mortem adult brain banks in Australia to operate with protocols specifically developed for brain cancer. Located within the Hunter New England Local Health District and operated by Hunter Cancer Biobank, the boundaries of service provided by the Brain Bank extend well into the surrounding regional and rural areas of the Local Health District and beyond. Brain cancer biobanking is challenging. There are conflicting international guidelines for best practice and unanswered questions relating to scientific, psychosocial and operational practices. To address this challenge, a best practice model was developed, informed by a consensus of existing data but with consideration of the difficulties associated with operating in regional or resource poor settings. The regional application of this model was challenged following the presentation of a donor located in a remote area, 380km away from the biobank. This required biobank staff to overcome numerous obstacles including long distance patient transport, lack of palliative care staff, death in the home and limited rural outreach services. Through the establishment of shared goals, contingency planning and the development of an informal infrastructure, the donation was facilitated within the required timeframe. This experience demonstrates the importance of collaboration and networking to overcome resource insufficiency and geographical challenges in rural cancer research programmes.

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Introduction

Brain cancers have extremely poor prognoses—more than two-thirds of adults diagnosed with glioblastoma survive less than 2 years post diagnosis.¹ The challenges associated with treating brain cancer are exacerbated by the relatively low profile of the disease and limited investment from the pharmaceutical industry.¹ However, funding for brain cancer research is now beginning to grow, possibly due to its rapidly increasing incidence worldwide,² recognition as the sixth leading cause of cancer in Australia,³ high profile cases of brain cancer^{4–6} and the establishment of philanthropic organisations such as the Mark Hughes Foundation⁷ and The Glioblastoma Foundation.⁸

Despite years of investigation, researchers are still plagued by an incomplete understanding of brain tumour biology,¹ resulting in substantial hurdles in biomarker driven research and the translational pathway. Limited progress towards improved histological and molecular diagnoses stem from siloed research

efforts and limited biological resources including access to human brain tumour tissue samples, hampering any large scale progress.⁹ Biobanks are an invaluable resource for biomarker and neuro-oncology research programmes, particularly when factors such as limited tumour size, varied histological subtype, methods of surgical resection and disparate preservation protocols may limit the collection of these specimens.¹⁰

Brain Cancer Biobanking

Brain biobanking has been identified as a distinct class of biobanking, with unique ethical, psychosocial, practical and logistical issues to be considered.¹¹ As recognised by Nusbeck et al,¹¹ post mortem brain donation is indispensable for neuropathological research, but it also raises certain questions regarding procurement, processing and storage. Many existing protocols have been informed by data obtained through mental health or neurodegenerative disease brain banking pilot studies.^{12–16} While



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there may be a degree of transferability for basic techniques, it stands to reason that the pathophysiological nature of brain cancer requires additional consideration outside this scope. At the heart of these considerations is post-mortem interval from death to deposition into the biobank, which while a primary consideration for all post-mortem donations involving the brain or other tissues, is particularly pertinent in brain cancer donations.

Among UK biobanks specialising in neurodegenerative diseases, a post mortem interval (PMI) of >72 hours is not uncommon and numerous publications document successful extraction of high quality DNA, RNA and protein from these samples as exemplified by Robinson et al¹⁴ and Durrenberger et al.¹⁷ We cannot, however, extrapolate these data to a brain cancer context given that PMI is exacerbated by disease specific factors such as prolonged agonal states, systemic hypoxia, increased intracranial pressure, tumoural molecular phenotypes and elevated rates of necrosis – all of which impact tissue viability.^{18,19}

The Mark Hughes Foundation Brain Biobank protocol has been developed to ensure maximal efficiency, aiming for an ideal post-mortem interval of <4 hours and maximum of 12 hours for difficult or regional cases. Based on existing literature, albeit extrapolated from models of neurodegenerative biobanking,¹²⁻¹⁶ this is considered to be sufficient for a high quality retention of DNA, RNA and protein. Paired samples are collected and stored as formalin fixed paraffin embedded blocks as well as fresh frozen tissue snap frozen in liquid nitrogen.

Logistical factors of transportation and 24-hour responsiveness are preliminary obstacles which require consideration in the development of a post-mortem brain donation programme. In addition to challenges relating to local health infrastructure, there are a number of legal and ethical requirements such as informed consent that are common to all brain donation programmes and must be carefully considered in order to avoid delays. An in-depth discussion of each factor is outside the scope of this commentary, however Australian, state based legislation, is largely covered by the Coroners Act²⁰ and Human Tissue Act 1983.²¹

One of the most difficult factors, irrespective of whether a brain biobanking programme is operating in a regional or metropolitan centre, is ensuring prompt certification of death. Legislation surrounding death and non-coronial autopsy in NSW, Australia, stipulates that prior to autopsy full certification of death must be documented, which involves examination of the deceased by a practicing medical practitioner to whom the patient is known.^{20,22} Time of death and death in the home further complicates this and often necessitates home visitation from a general practitioner or palliative care physician out of hours, a process which in many cases exacerbates delays or can result in law enforcement at the scene should advanced care directives not be completed sufficiently. Further adding to delays, legislation stipulates that ongoing consent must be

sought from next of kin once the patient has passed away, a process undertaken by a designated officer located within the hospital.²¹ Once these processes are completed and the patient has been transported by local funeral services to the mortuary, there is often minimal time remaining to complete the donation process.

In a fully resourced setting the above factors present substantial challenges with respect to a 4 hour window, however in a resource poor or regional community these obstacles can appear insurmountable. The remote nature of medical facilities and residential properties alike necessitate the need for robust patient transport services, however in many of these communities, transport services are limited in both availability and frequency.²³ A concerted effort has been made in recent years to increase palliative care services in regional areas in Australia, however limited resources and excessive travel times often result in a reduced provision of care, which is particularly concerning when death in the home is not uncommon for patients in these communities.^{24,25} The same can be said for general practitioner services with many patients traveling long distances to access services.²⁶

Given many rural patients experience challenges accessing medical services, it is unsurprising that they also have reduced exposure to medical research opportunities.²⁷ This has implications for population and sample diversity in a research context but also results in an inequity for patients who may wish to contribute, or may even gain psychological benefit from participating in medical research.²⁸

While certain geographical challenges are unavoidable, infrastructural challenges can be overcome with planning, networking and communication – demonstrating that even the most intricate medical research protocol can be extended into a rural or resource poor setting.

Example Case Study: A Rural Challenge

In late 2018 the Mark Hughes Foundation Brain Biobank was notified of a potential donor who had previously been treated in John Hunter Hospital (Newcastle) before returning to his home community in rural New South Wales (NSW). The patient wished to pass away on the family property, located 20 minutes from the nearest hospital, 5 hours' drive from the Brain Biobank located on the same campus as the John Hunter Hospital.

The patient passed away during business hours and while the palliative physician was en-route for a routine visit and therefore able to provide certification of death promptly. Certification, by an appropriate physician, be it a palliative care physician, general practitioner or emergency care physician, is required to commence the donation process. Certification occurred in the home and the patient was transported by NSW Statewide Patient Transfers who have vehicles roaming rural areas for long distance transport and were 3 hours away at the time of death. Brain donation was completed in Newcastle

within 11.5 hours and the deceased was transported back to their home community by NSW Statewide Patient Transfers the following morning. Numerous challenges were assessed and overcome during the planning stages of this donation which can be broadly considered as follows:

Psychosocial challenges

Ensuring informed consent is obtained is fundamental to any tissue donation programme and establishing relationships with donors is a core aspect of this. Informed consent is an ongoing process and for our programme this involves numerous conversations and meetings between biobank representatives, health care professionals, potential donors and their next of kin. Wherever possible these are held face-to-face and then supported by follow-up telephone and email communications. Secondly, to ensure a smooth donation process it is essential that next of kin are engaged early in the process. Regardless of agreements put in place between the donor and the biobank, next of kin retain the right to withdraw consent at any time following death and in this instance the donation cannot occur.²¹ For this reason, establishing a trusting relationship with next of kin is paramount to ensure that planned processes are carried out despite the acute onset of grief. While senior next of kin are supported to withdraw consent should they wish, 100% of consented donors for the Mark Hughes Foundation Brain Biobank have completed the donation process to date.

Legal and ethical challenges

A number of legal and ethical challenges were acknowledged in this situation, largely around the completion of advanced care directives, informed consent documents, non-coronial autopsy authorisation and expected death at home certificates. Completion of documents such as advanced care directives often requires discussions prior to end-stage disease for this cohort of patients. It is not uncommon for first contact with potential donors and their families to occur in the later stages of disease. Anecdotally our experience indicates that while brain donation is a consideration for patients throughout their journey, the decision to engage with the donation team is often not made until they reach end-stage disease. In other cases, contact can be made almost immediately following diagnosis, however at this early stage decisions around the planned location of death are somewhat premature and need to be approached with sensitivity. The final decision for a donor to pass away at home is often not made until the patient reaches advanced stages of disease, which can occur suddenly, and the associated cognitive and functional decline make the timely completion of advanced care directives difficult. The brain donation team introduce the importance of advanced care directives and provisions for home death in early conversations, encouraging a 'just in case' philosophy, however the process is

fluid and decisions are often made and changed numerous times prior to the patient passing.

In this instance, early contact with the patient and their family was made, however the decision to die at home was made suddenly and following rapid deterioration. Further complications arose with regards to the patient's treating physician, given their treatment had been in a different local health district to the one in which they were now residing. As such, there was no established relationship with a local general practitioner to facilitate rapid completion of advanced care directives such as an expected death in the home certificate.

One of the greatest challenges however was the anticipated completion of the death certificate and the requirement that this be completed prior to autopsy, following examination by a medical practitioner to whom the patient was known.

Logistical challenges

No appropriate mortuary facilities were available locally preventing the donation occurring within the donor's local community. Air transportation was not an option due to limited resources. Statewide Funeral Transfers services provided a viable option, however their nearest port was within 4 hours of the patient, taking the total transport delay to 9 hours unless an operator was, by chance, roaming in the vicinity.

Innovation and Informal Infrastructure Development

Operating across local health districts results in a number of challenges, further exacerbated by the challenges of operating within a rural context with reduced resources. Our approach to facilitating this request and confronting the aforementioned challenges can be assessed in 4 stages.

Assessment of local infrastructure

Having established an operational system within our own local health district, initial assessments were conducted to identify equivalent services. Table 1 outlines the core services employed within our current network along with our findings regarding equivalent services.

Relationship building

Relationships with medical, administrative and allied health professionals external to the brain donation team are essential for programme delivery. In many instances these individuals operate outside the scope of their regular roles to ensure patient wishes are acted upon and the programme is completed within the required timeframe.

The establishment of shared goals with third parties such as palliative care physicians and funeral transport operators was therefore key to delivering this programme, particularly when much of the contribution required pushed the boundaries and

Table 1. Service equivalency investigations.

SERVICE REQUIRED	RATIONALE	AVAILABLE SERVICES
General practitioner with 24-hour availability	Prior to the removal of a deceased patient from the home, certification or validation of death must be conducted by a physician to whom the patient is known.	GP located 1 hour away from patients' home, no ongoing contact with patient following referral to palliative care services.
24-hour palliative care services – available physician or nurse	In the absence of a general practitioner, a palliative care physician to whom the patient is known can certify death in the home.	No medical/physician palliative care services after hours.
	In the absence of a physician, a palliative care nurse can provide a validation of death and enable patient transport to relocate the deceased to a hospital for certification by a physician.	Limited availability of palliative care nurses. Telephone advice only after hours.
Mortuary facilities to enable local non-coronial autopsy within 4 hours	To reduce post-mortem interval, autopsies can be performed locally if an appropriate facility is available and the brain donation team can be granted access.	No autopsy facilities in the local area
24-hour patient transport services with immediate dispatch	Patient transport must be available to transport the deceased from the home to the autopsy facility as soon as certification is complete to avoid lengthening the post-mortem interval.	Available, Statewide Funeral Transfers services. Drivers roam between calls and could be in transit or in port at the time of death. Nearest port for dispatch 4 hours from patients' residence. Possibility for driver to be in closer or further proximity depending on situation at time of death.
24 hour emergency department	In the absence of a physician able to attend the home, patients can be transported to the emergency department for certification of death, provided a palliative care nurse or ambulance officer/paramedic has completed a life-extinct or validation of death certificate.	Available

scope of professional responsibility. Through engagement, education and ongoing communication we encouraged our rural partners to take ownership of the process and to professionally invest – a process made possible given the existing relationship between the health care providers concerned and the donor patient. The responsiveness of the local community and the willingness to engage with our programme reinforced our impressions of rural attitudes to collaboration. Whether this could be replicated in a larger metropolitan community with formal structures remains questionable.

Establishment of informal structures

In conjunction with the establishment of relationships is the need to ascertain the willingness of health care providers to engage with the programme outside the scope of usual clinical responsibilities. Most commonly, this involves the delivery of services outside the normal hours of service provision. Given the limited resources available within this setting our programme operated well outside the bounds of professional obligation and, riding on the relationships discussed above, involved informal modes of communication to enable out-of-hours contact and ensure service delivery.

Contingency planning

Given the informal nature of our newly established infrastructure, it was recognised that contingency planning was essential. Numerous scenario-dependent protocols were established

including alternative plans for certification of death, patient transport and the involvement of emergency services. Figure 1 illustrates a core scenario dependant protocol in place for certification of patient death.

Discussion

Rather than working within a system fraught with potential obstacles we chose to work in the outer boundaries of the system, relying on communication and the establishment of shared goals to supplement scarcity of infrastructure.

Ongoing communication and engagement with core stakeholders allowed us to develop an informal network that supplemented the existing infrastructure, enabling a highly demanding protocol to be offered without the support of essential services. The current resources available to this community did not allow for 24-hour engagement, nor was there infrastructure in place to support an expansion of this kind. As such, we appealed to individual service providers to gain their support on a personal level, rather than an operational level and found that through this approach, out of scope engagement was far more easily attained.

This has subsequent implications regarding the ability of health services to increase equitable access to research programmes for rural and resource poor communities, indicating a willingness to support such programmes. We do recognise that this is an isolated case, however, and that repeated attempts at relying on altruism without increased financial and resource support for these services would likely result in reduced responsiveness from health service providers.

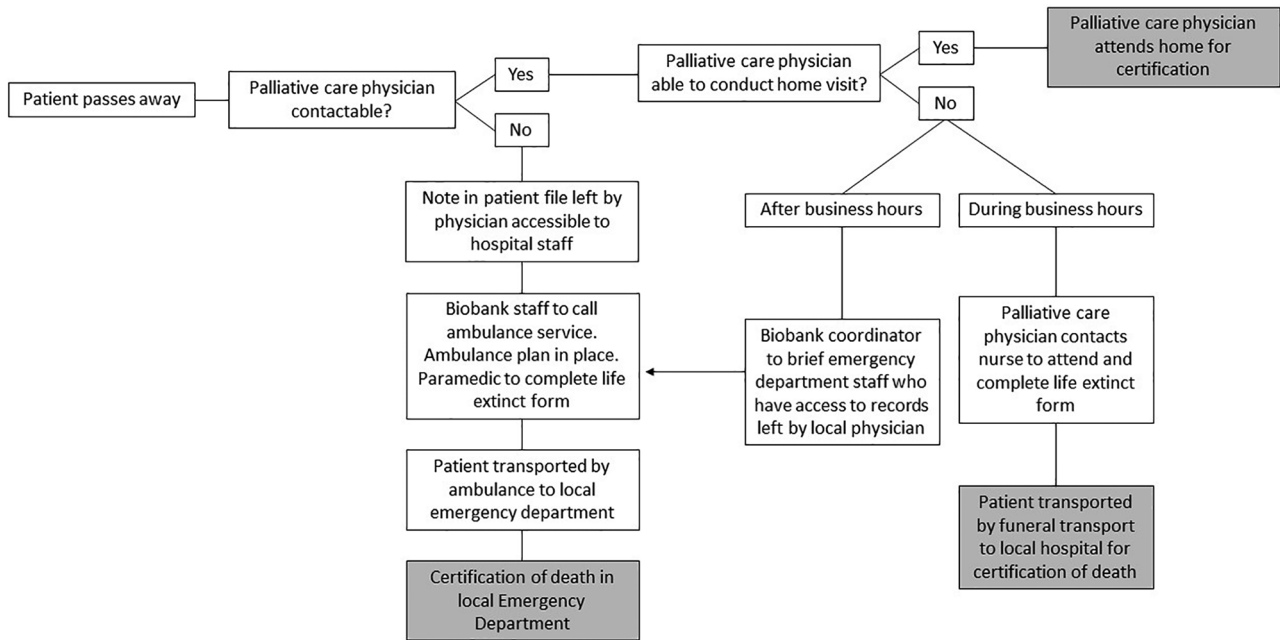


Figure 1. Demonstrates scenario dependant outcomes based on availability of palliative care staff at the time of patient death.

Internationally, similar challenges are noted given declining autopsy rates in all affluent countries – largely due to changes in autopsy governance,^{29,30} but also due to lack of infrastructure. A Dutch study examining autopsy rates over a 35-year period identified a vast decline, citing scarce healthcare resources and a lack of prioritisation of autopsy facilities and staff as a key contributing factor.³¹ The reduction in support for autopsy facilities poses a huge challenge for brain banks that cannot be overcome with altruism alone, however Blokker et al³¹ also cite cost reduction policies and pathologist resistance to autopsy as causative factors.

Within the American system challenges may be faced with respect to federal and inter-state legislation and variations in policy regarding next of kin authorisation for autopsy, despite the Uniform Anatomical Gift Act.³² As is recognised by Hooper et al,³³ advance transportation and logistical planning can be individually arranged with out-of-state funeral homes local to home hospice patients on a case-by-case basis. Given many states face the same geographical challenges as regional Australia, the attendance of a physician or palliative care nurse for legal pronouncement of death in the home can be problematic, particularly with the added complication of privatised healthcare.

The failure of formalised systems and the value of informal networks is clearly demonstrated within the German healthcare system, not only with respect to brain donation but most evidently with respect to organ donation for transplantation. Between 2010 and 2018 the number of organ donations across Germany fell by more than 30%.³⁴ Studies indicate that while the number of potential donors increased during this period, the number of contacts with the German National Organ Transplantation Foundation (DSO) decreased by 18.7%.³⁵

Interestingly, in August 2012 the amendment to the Transplantation Law came into effect, requiring all hospitals to designate an individual responsible for transplantation and to report potential organ donors to the DSO. Counter-intuitively, once this law was in effect, the number of reported potential donors decreased by a further 6.1% – postulated to be a result of uncertainty generated by a lack of guidelines specifying when and how potential donors were to be reported within the new system.³⁴ Perhaps most interestingly, a subset of hospitals who voluntarily participated in DSO coordination projects saw a 3-fold increase in DSO reporting – largely attributed to the motivations of individual staff.³⁴

To rectify the situation, further legal amendments to the national structural framework for organ donation were implemented in 2020. This move indicates a clear recognition of the need to provide adequate resources and financial support for transplantation, while also fostering collaboration and human-centred coordination for what is intrinsically a patient-centred programme.³⁶ This paradigm serves as a gold standard for brain banking programmes, demonstrating the possibilities presented by a well-funded and supported system, operated by enthusiastic, engaged and networked staff who are afforded sufficient flexibility to take a personalised approach to donors. Our hope is that with increased knowledge translation from banked samples, brain banking will receive similar support to that afforded transplantation in the coming years – both in Germany and internationally.

In contrast to questions of optimising infrastructure is the notion of true resource scarcity examined with respect to the international climate. The last reported tally indicates there are only 5 low-middle income countries who have formal brain banking operations.³⁷ Prior to the establishment of the Ibadan

Brain Ageing, Dementia and Neurodegeneration (IBADAN) programme in 2019, there were no established brain banking programmes on the African continent.³⁸ While funding and resource scarcity are expected challenges in this setting, Akinyemi et al³⁸ cite differences in cultural and religious beliefs, shifts in societal dynamics, lack of infrastructure and declining autopsy rates – which are in part attributed to distrust of the health system. Given these challenges of resource scarcity, cultural diversity and a compromised relationship between the community and medical establishment, a standardised formal protocol may not be sufficient for operational purposes. The authors reference extensive engagement with community, religious leaders and patient advocacy groups as the core to the establishment of their programme, and from this we can infer recognition of the need to tailor approaches to individual sub-populations and communities to maximise donor recruitment. This implies the most appropriate model of operation in this setting is one that is fluid, personalised and can account for various degrees of diversity and resource scarcity – somewhat incongruent from the idyllic, stringent and formalised protocols more frequently employed for patient recruitment. The implementation of brain banking efforts in low-middle income countries such as Nigeria demonstrate the invaluable nature of flexibility and informal systems for successful brain banking.

Our philosophy in working within the informal boundaries of the system is 2-fold; the provision of a service for patients and researchers alike, but also the engagement of key stakeholders within the patient community and health system who can add weight to the argument that further support for properly implemented infrastructure programmes is necessary.

In Australia, recognition of the need to advance research into brain cancer is topical due to the efforts of several high-profile community members working to raise awareness.^{7,39} While grassroots in scale, our programme is working to ensure that optimal biological resources will be available for use by the wider research community. Simultaneously, the scoping work conducted through the ongoing, real-world operation, of our programme is contributing to a better understanding of the requirements of a brain cancer rapid autopsy programme. Ultimately, the basis of a best practice model that could be employed internationally.

The aim of our programme is that through continual engagement with health services and the ongoing provision of samples into translational research programmes, these samples will contribute to an expansion in the understanding of brain cancer biology. Changes in practice that result from an increased understanding of brain tumour biology will necessitate further investment into translational research programmes and the infrastructure that support them.

Conclusion

Our protocol demonstrates the ability of teams to deliver demanding research services and complex protocols in spite of resource and infrastructure insufficiency, provided


high-level planning, communication and collaboration underpin all processes. As such, we have extended the opportunity for patients and families in these communities to contribute to an enduring legacy that will benefit the research community and subsequently lead to improved outcomes for people with brain cancer – promoting equity for engagement in research, irrespective of postcode.

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