What is the background on the Brain Tumour Research Study?

The treatment of brain tumours is ultimately determined by the diagnosis made through a microscope by a neuropathologist who assesses the appearance of the brain tumour after it has been removed by the neurosurgeon. In an individual patient, these microscopic criteria do not always accurately predict either a brain tumour's behaviour (how quickly it will grow, progress or spread), causation or its response to treatment. Brain tumour pathologists may also disagree on microscopic diagnoses. Where there is disagreement there is uncertainty about how to manage patients with brain tumours.

Fortunately, the last 10 years have witnessed spectacular advances in our understanding of the molecular events (those cellular events which happen at the level of tumour DNA / RNA and which involve the proteins that are encoded by DNA) involved in the origin, growth and spread of tumours through the brain. Increasingly, it is becoming apparent that brain tumours may, like breast tumours, be grouped according to the presence or absence of specific 'biomarkers', usually genetic, and indeed cancer specialists have already begun to recognise certain groups of brain tumours whose prognosis is determined by the presence or absence of specific tumour related genetic markers.

However, the pivotal role of genetics in the day to day management of adult brain tumours lags some way behind the critical role played by genetics in patients with more common cancers such as breast. Here in Beaumont Hospital we have access to carefully archived brain tumour tissue specimens from over 9000 patients. In collaboration with Genuity Science (formerly Genomics Medicine Ireland (GMI)), it is our goal to re-assess these archived brain tumour samples using new genomic analytic methods to see if we might have better predicted a brain tumour's behaviour and response to treatment and so inform our thinking about how to manage future patients with brain tumours in the years ahead.

To do this, we plan to apply the most sophisticated genetic technologies complemented by powerful bioinformatics analysis to study the large brain tumour sample collection currently archived in Beaumont Hospital. Our goal is to create an interactive database or **Brain Tumour Information System (BTIS)** incorporating

all tissue-based data (microscopic & genetic) together with health data (demographic, radiologic and survival data) which can be used as the basis for predicting behaviour of brain tumours in patients in the years to come.

Beaumont Hospital has already participated in building the most comprehensive Childhood Brain Tumour Information System currently available to oncologists and pathologists *(Capper et al., DNA methylation-based classification of central nervous system tumours. Nature. 2018;555(7697):469-474*). The scope of the current project is to mirror this work in adult patients with brain tumours.

Who is organising and funding this study?

Beaumont Hospital is carrying out research into brain tumours and has established a research collaboration with Genuity Science (formerly Genomics Medicine Ireland (GMI)), a privately funded Irish life sciences company, which researches the human genome to examine the relationship between genetics, health and disease. Genuity Science is funding sequencing and associated costs in connection with this study. Original ethics approval for this brain tumour study was granted by Beaumont Research Ethics Committee in 2016.

What is meant by surplus tissues and how can they be used?

A surgeon will always try to remove as much abnormal tissue as is safe to do. Only a small fraction of the removed diseased tissue is needed to make a pathology diagnosis. Well-characterised human tissue specimens are a pillar of human disease research, not just in cancer and dementia research, but in many other areas such as renal disease. Recent technological advances have made it much easier to extract and sequence DNA and RNA from formalin fixed paraffin embedded tissues. Never have pathology researchers had access to such incredibly powerful investigative tools, which combined with information on a cancer's behaviour including response to treatments and survival can yield vital information as to why some patients have done well, while other patients with a virtually identical cancer have not fared so well.

Armed with this historic biological information, the aim is to provide future patients with personalised treatments that do not require a patient to enter a long-term trial, sometimes not even knowing if they are receiving a useless placebo or a potential lifesaving drug.

Pathology departments are the recognised legal caretakers of all archived tissues and, as such, must always abide by hospital and national regulations. Pathology departments will always ensure that adequate diagnostic material remains in the tissue block for future testing and for independent consultation, or when required for medico-legal issues.

What is the value of surplus tissues in research?

Unlike tissue samples collected specifically for research, these surplus diagnostic formalin fixed paraffin embedded blocks occupy a unique bioethical niche. Surplus tissue blocks have enormous research value, especially for clinical and translational research, since they can be linked to information on diagnosis, treatment response, and disease outcome contained within pathology and hospital databases.

The last 5 years have seen a huge increase in the use of formalin fixed tissues because of their convenience, availability, numbers, exchangeability and ease of biomarker validation. These tissues are underpinning today's precision medicine and the quest for new personalised treatments.

Why can't consent be obtained for use of archived tissues in research?

Attempting to obtain consent for the use of even a few of the 7 million tissue specimens that exist in pathology departments across Ireland is beyond the resource capability of these departments. In practical terms, trying to obtain consent but not knowing whether a patient is alive or deceased is extraordinarily challenging, with great potential for causing patient and family distress, as has been shown with previous re-consent attempts in Ireland.

Previous research into patients' disposition to the use of archived diagnostic tissues confirms a philanthropic attitude on behalf of the donors of such tissues (*Richter et al., Patient Views on research use of clinical data without consent: Legal, but also acceptable? EJHG 2019; 27, 841–847)*, provided of course that the research is carried out to further disease knowledge in the public interest and which has been approved by a Research Ethics Committee, as has this study.

Much tissue-based investigative laboratory work consists of audit to ensure that pathologists are practicing to an acceptable level of expertise. Fundamental research, where pathology researchers use archived tissues to make improvements or to uncover new disease pathways is the pillar that underpins standards in healthcare.

What will happen to the surplus tissue samples that may be used in the research project?

DNA and RNA will be extracted from surplus tissue samples, and advanced techniques will be carried out, such as whole genome sequencing and RNA sequencing, which are laboratory processes that determine which of our genetic instructions are turned on or off at a particular time. This will help to identify which genetic changes contribute to the causation and/or progression of brain tumours, as well as helping to develop new drugs and therapies to treat brain tumours.

Genuity Science (formerly Genomics Medicine Ireland (GMI)) has established Ireland's first purpose-built genome sequencing laboratory at its headquarters in Dublin, and samples will be sent to this facility for sequencing to inform this study. Genuity Science's genome sequencing laboratory is accredited by the College of American Pathologists (CAP) which is an internationally recognised accreditation board and widely considered the leader in laboratory quality assurance.

Am I identifiable from the personal data used in this study? What personal data of mine will be used in this study?

The creation of the BTIS requires that genomic data (generated by sequencing the brain tumour sample) be combined with **de-identified** information from the patient's

medical notes, such as gender, age and information relating to the brain tumour (location, size, behaviour etc).
Health information will be stripped of any personally identifying data points (name, date of birth, address, contact number etc), therefore it will never be possible for Genuity Science (formerly Genomics Medicine Ireland (GMI)) or any future researchers to link back any findings to individual patients.
Beaumont Hospital has in place a comprehensive suite of measures to protect the personal data of its current and former patients.

For the purposes of this study, all relevant participant data and brain tumour samples will be assigned a random study ID number at Beaumont, before being shared with Genuity Science for sequencing and inclusion into the BTIS. Once the data has been incorporated into the BTIS, the link between the hospital ID and random study ID will be promptly broken. This process renders the data de-identified and masks the participant's identity. Personal identifiers, such as the participant's name or date of birth, are never used to label the participant's samples or clinical information.
Genuity Science has a very high level of technical and organisational measures in place to protect your de-identified data from unlawful or unauthorised access or disclosure.

How will my data be accessed and used?

The overall aim of this study is to create an interactive database (the Brain Tumour Information System or the "BTIS"), incorporating all tissue-based data (microscopic & genetic) together with health data (demographic, radiologic and survival data), which can be used as the basis for predicting behaviour of brain tumours in patients in the years to come.
All data stored in the BTIS is de-identified and cannot be linked back to an individual by any party accessing the BTIS, other than Beaumont.
Both Beaumont and Genuity Science (formerly Genomics Medicine Ireland (GMI)) will have access to the BTIS for interrogation (ie raising queries against the data in the BTIS).

Beaumont will access the BTIS for future patient care, academic research and teaching.

Genuity Science, its authorised research partners, including academic and commercial partners (such as academic institutions, pharmaceutical or biotech companies), will access the BTIS for commercial and academic research projects. Access is strictly controlled and carefully restricted.

Before Genuity Science's authorised research groups can access the BTIS, Genuity Science will enter into legal agreements with these third parties, which will strictly control their activities and prohibit them from downloading the BTIS data.

When the relevant authorities have formulated public policy in relation to publication and sharing of genomic data, the BTIS will be made publicly available on a recognised genomic data repository in a de-identified and appropriately controlled way and in compliance with all relevant legislation.

The results of the research study will be published in peer reviewed journals.

How long will my data be kept and used for?

Your de-identified data will be incorporated into the Brain Tumour Information System will be retained indefinitely and used for the benefit of future patients at Beaumont Hospital and for research by Genuity Science (formerly Genomics Medicine Ireland (GMI)) and its research collaboration partners.

Continual analysis is necessary as medical and technological changes and advances emerge over time and the data collected may gain new significance.

What are the possible benefits of participating?

Participating in this study will not benefit you directly. You will not receive any results or feedback from this study. However, information obtained from the study may help us to better understand brain tumours and to improve diagnosis and treatments of patients in the future.

What are the possible risks of taking part?

As the health data in this study has been de-identified, any risks of discovering health-related findings or any impact on personal insurance have been effectively removed. There are no therapies used in the study and therefore therapy associated risks do not arise.

What is the deadline for opting-out of the study?

Opt-out from this study is possible until 31st December 2020.
After this date, it will not be possible to request to opt-out from the study.

Who has this study been reviewed by?

The study has been reviewed and approved by Beaumont Research Ethics Committee, based on a waiver of consent.

With regards to consent for the use of data for the study in accordance with data protection legislation, the study received a conditional consent declaration has been made under the Health Research Regulations 2018. A number of conditions have been attached to the consent declaration, including a condition that a publicity campaign would commence to highlight the study and enable patients and families to withdraw their data from the study.

Brain Tumour Ireland have also provided their input into the conduct of this study and patient engagement.

How do I know if I am an "appropriate" relative?

If you are a relative of a deceased brain tumour patient who attended Beaumont Hospital between 29th November 1987 and 7th August 2018, you can request to have their archived brain tumour sample excluded from this study if you wish.

When you contact Beaumont (at the address listed above), hospital staff will ask you to provide some information relating to your deceased relative, which will enable the Beaumont team to verify your identity and your relationship to the deceased. Once

you have been verified as an appropriate relative, the opt-out request will be processed.