What is genomics?

Genomics is the study of our genes - the DNA contained in the cells of our body that acts as a blueprint for a human being. Each of us has a slightly different DNA sequence that sets out who we are, how we work… and even how we can be repaired. Studying our DNA can help us understand an amazing range of health-related characteristics, including:

- understanding disease risk;
- predicting our response to medications;
- pointing the way to new treatments and cures.

The famous double-helix structure of our DNA contains a lot of information; there may only be four building blocks in the structure (A, C, G and T) but every strand of our DNA contains 3.2 billion of these letters.

Technological advances mean we can now decode a person's genome in days, compared to the 13 years it took to complete the first ever genomic map. This has made genomic research a viable and revolutionary new front in the pursuit of improved human health.

Tumours have their own unique sets of genes that usually bear little or no relationship to the genes inherited from a parent. We know that the study of all of the genes within a tumour can tell us so much more about how a tumour will grow and spread and how it may or it may not respond to treatment or indeed whether the tumour should be exposed to treatments that may injure the patient but have little or no effect on the tumour.

How this massive amount of information influences the behaviour of a tumour can only be fully understood if we have access to the genetic techniques that can deliver the order of every letter in the book, so called whole genome sequencing. This massive amount of information, which can only be processed by dedicated software programmes, is only of use if we know how the tumour from which we derived the sequence has already behaved.

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 (so-called surplus tissues) from over 9000 patients. In collaboration with Genuity Science (formerly Genomics Medicine Ireland (GMI)), it is our goal to re-assess these archived surplus 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.

Furthermore, through Genuity Science's collaboration with commercial and academic research partners using the de-identified tissue-based data (microscopic & genetic) together with health data (demographic, radiologic and survival data), Genuity Science hopes the insights gained through its studies will lead to the development of new treatments and diagnostics for brain tumour patients. Genuity Science's commercial partners include pharmaceutical and biotech companies who develop new diagnostic tests, identify new risk factors or drug targets, and develop, test and market new drugs.

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, a global life sciences company. Genuity Science, formerly known as Genomics Medicine Ireland (GMI), was founded in Dublin in 2015 and in 2018 was acquired by WuXi NextCODE, headquartered in the Boston area.

Genuity Science carries out research on the human genome to examine the relationship between genetics, health and disease by working closely with clinics, universities and commercial partners. All costs associated with the establishment of the BTIS are being funded by Genuity Science.

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 tissues that have been prepared for clinical review by a pathologist. Surplus tissues 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. 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.

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 will we do with your surplus tissue?

Having first made sure that an adequate amount of tissue will remain in your tissue block, we will take thin sections from your tumour and place them into a transport medium within a test tube. The Beaumont identifying number will be replaced by a unique study number on the test tube before the sample is sent to Genuity Science for sequencing.

DNA and RNA will be extracted from the 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.

Information about your tumour size, location, rate of growth and its radiological appearance will be taken from the pathology, radiology and clinical files at Beaumont, and will also be shared with Genuity Science. Personally identifying information such as your name, date of birth, address, place of birth, ethnicity, hospital number, will never be shared with Genuity Science, or any of their collaborators.

In the future we hope to carry out up-front genetic testing on the brain tumours in new patients and compare this genetic information with the genetic signature of your old tumour, whose behaviour has already been well established. This will help us better able to predict how the new tumour of new patients will behave and will help in deciding the treatment options for future patients with brain tumours. Predicting a tumour's behaviour by how it looks down the microscope will no longer be acceptable practice. By allowing your tumour to be used in this study you will be helping new patients for years to come.

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

The samples that will be used in this research have been collected by Beaumont Hospital pathology department over more than a 30 year period. 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. Given that many of these archived tissue samples were collected over thirty years ago, an unknown (but likely very high) number of patients are deceased. The prognosis of Glioblastoma Multiforme (one of the primary tumour types contained within the collection) is very poor whereby 95% of patients are deceased within 30 months of diagnosis. In addition, given the

long period of time, many patients will have changed address, and we have no way of identifying what their new address could be. .

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 audits to ensure that pathologists are practicing to an acceptable level of expertise. Fundamental research, where pathology researchers use archived surplus tissues to make improvements or to uncover new disease pathways is the pillar that underpins standards in healthcare.

The Health Research Regulations, which were introduced as part of the Data Protection Act in 2018, recognise that sometimes, in limited situations, obtaining consent will not be possible and that the public interest of doing the research significantly outweighs the need for explicit consent. The Health Research Regulations established a process to obtain a Consent Declaration in such circumstances. In line with this process, the BTIS study was reviewed independently and a Consent Declaration was granted in September 2019.

What data is collected and used as part of this study?

The creation of the BTIS requires that **de-identified** genomic data (generated by sequencing the brain tumour sample) be combined with **de-identified** health information from the patient's medical notes, such as gender, age and information relating to the brain tumour (location, size, behaviour etc).

The health information provided to Genuity Science will not contain any personal information such as name, date of birth, address, contact number, so that the risk of anyone (including Genuity Science and its collaborators) re-identifying a patient from the de-identified genomic or health information is minimal.

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 and irreversibly broken. This process de-identifies the data.

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.

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

Genuity Science will also retain a copy of the de-identified genomic data and health information for their commercial research studies into the genomic basis of brain tumours. Through their collaboration with commercial and academic partners, Genuity Science hopes the insights gained through its studies will lead to the development of new treatments and diagnostics for patients with brain tumours. Genuity Science's commercial partners include pharmaceutical and biotech companies who develop new diagnostic tests, identify new risk factors or drug targets, and develop, test and market new drugs. Information regarding the partners that Genuity Science will be working with in the future will be made available on the Genuity Science website (www.genuitysci.com) once those partnerships are in place.

All de-identified study data retained by Genuity Science will be held in Genuity Science's secure database (which is stored in Ireland). Access to Genuity Science's database is strictly controlled and carefully restricted.

Before Genuity Science's commercial and academic partners can access the study data in the Genuity Science database, Genuity Science will enter into legal agreements with these third parties, which will strictly control their activities and prohibit them from downloading any study data from Genuity Science's database.

When the relevant authorities have formulated public policy in relation to publication and sharing of genomic data for research, 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 and will be retained indefinitely by Beaumont Hospital and used for the benefit of future patients at Beaumont Hospital.

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

Genuity Science will retain its copy of the de-identified study data for so long as its research projects with its academic and commercial collaborators into the genomic basis of brain tumours are ongoing. Genuity Science will regularly assess the ongoing retention of the study data to ensure there is a clear necessity for continued retention for the purpose of carrying out its research projects.

What are the possible benefits of participating?

Participating in this study will not benefit you directly. As all data used in the research will be de-identified, 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.

The benefits of this approach for children with brain tumour is already well developed through the work of colleagues in Heidelberg, Germany which has since 2016, transformed the diagnosis and management of children with brain tumours. Beaumont Hospital is in a unique position to develop this approach to the diagnosis and management of brain tumours in adults.

Furthermore, through Genuity Science's and Beaumont Hospital's collaboration(s), jointly and independently, with commercial and academic research partners using the de-identified tissue-based data (microscopic & genetic) together with health data (demographic, radiologic and survival data), we hope the insights gained through such studies will lead to the development of new treatments and diagnostics for brain tumour patients.

Genuity Science's commercial partners include pharmaceutical and biotech companies who develop new diagnostic tests, identify new risk factors or drug targets, and develop, test and market new drugs.

What are the possible risks of taking part?

As explained in the section "**What data is collected and used as part of this study?**", the tumour samples and health data in this study will be de-identified, any risk of re-identification of a participant from the data is minimised.

Will it be possible to use the findings of this study to learn more about familial brain tumours?

As the study data is de-identified, it will not be possible to relate any of the findings of this study back to patients who may have a family history of brain tumours. If you would like to learn more about the risks that exist in your family for brain cancer you should contact your doctor to discuss.

Who has this study been reviewed by?

The study has been reviewed and approved by Beaumont Research Ethics Committee.

This study has also received a conditional consent declaration from an independent Appeals Panel in accordance with the Health Research Consent Declaration process established by the Health Research Regulations 2018.

Will the data be shared outside the European Economic Area (EAA)?

As permitted by the Conditional Declaration granted by an independent Appeal Panel in accordance with the Health Research Consent Declaration process established by the Health Research Regulations 2018, Genuity Science will allow its academic and commercial partners (whether or not they are located in the EEA) to access the de-identified study data stored in its database under strictly controlled conditions. Genuity Science's research partners cannot download any patient's data from the Genuity Science database. The Appeal Panel in arriving at its decision to grant a conditional declaration specifically noted its satisfaction that the steps taken by Beaumont and Genuity Science to protect the confidentiality of patients would adequately protect the privacy rights of the study participants.

In accordance with the Conditions attached to the HRCDC Declaration, the BTIS will eventually 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.

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

The deadline for opting-out from this study has been extended until 1st April 2021. Due to the de-identification of all samples and data used in the study, it will not be possible to request to opt-out from the study after this date.

How do I withdraw or opt-out of this study?

Living Patients

If you were a brain tumour patient at Beaumont Hospital within the time period, 29 November 1987 and 7th August 2018, you may request that your samples and data are not included in the research.

Deceased Patients

If you are a family member/relative of a deceased patient who was a brain tumour patient at Beaumont Hospital within the time period, you may request that your family member's samples and data are not included in the research.

Simply contact Beaumont Hospital at btis@beaumont.ie or by phone at 01 797 7726 before 1st April 2021. After this date, it will not be possible to be excluded from the research.

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.