GeCIP Detailed Research Plan Form

Background

The Genomics England Clinical Interpretation Partnership (GeCIP) brings together researchers, clinicians and trainees from both academia and the NHS to analyse, refine and make new discoveries from the data from the 100,000 Genomes Project.

The aims of the partnerships are:

1. To optimise:

- clinical data and sample collection
- clinical reporting
- data validation and interpretation.

2. To improve understanding of the implications of genomic findings and improve the accuracy and reliability of information fed back to patients. To add to knowledge of the genetic basis of disease.

3. To provide a sustainable thriving training environment.

The initial wave of GeCIP domains was announced in June 2015 following a first round of applications with expressions of interest in January 2015. In April 2016 we invited the inaugurated Cancer GeCIP domains to develop research plans for 'Gear 2' working closely with Genomics England. Within the Cancer Main Programme, the 'Gear 2' phase of the project refers to recruitment of specific cohorts of patients, inclusion of biopsy tissue (diagnostic/recurrence) and ctDNA in selected cohorts and the initiation of clinical trials in early stage (adjuvant/consolidation) setting. These will be used to ensure that the plans are complimentary and add real value across the GeCIP portfolio and address the aims and objectives of the 100,000 Genomes Project. They will be shared with the MRC, Wellcome Trust, NIHR and Cancer Research UK as existing members of the GeCIP Board to give advance warning and manage funding requests to maximise the funds available to each domain. However, formal applications will then be required to be submitted to individual funders. They will allow Genomics England to plan shared core analyses and the required research and computing infrastructure to support the proposed research. They will also form the basis of assessment by the Project's Access Review Committee, to permit access to data.

Domain leads are asked to complete all relevant sections of the GeCIP Detailed Research Plan Form, ensuring that you provide names of domain members involved in each aspect so we or funders can see who to approach if there are specific questions or feedback and that you provide details if your plan relies on a third party or commercial entity. You may also attach additional supporting documents as relevant (optional).

Additional members can apply to join the GeCIP domain by completing the form on our website found here: http://www.genomicsengland.co.uk/join-a-gecip-domain/.

Genomics England Clinical Interpretation Partnership (GeCIP) Detailed Research Plan Form

Application Summary	
GeCIP domain name	**Glioma Cancer**
Project title *(max 150 characters)*	**Glioma cancer research in the 100,000 Genomes Project**

Objectives. *Set out the key objectives of your research. (max 200 words)*

1. Somatic driver gene identification.
2. Complementary analyses;
    a. Further analyses of DNA
    b. RNA and protein studies
3. New classifiers of glioma based on molecular features, histology and patient characteristics
4. Cross-cutting analyses

Lay summary. *Information from this summary may be displayed on a public facing website. Provide a brief lay summary of your planned research. (max 200 words)*

Gliomas are tumours of the central nervous system (the spine or brain) starting in a particular type of cell called glial cells. They are the third and sixth most common tumour in middle-aged men and women respectively. Gliomas are heterogeneous with various different subtypes being identified, and these differences reveal themselves in differing responses to therapy and differences in survival rates. Typically gliomas are associated with a poor prognosis or outcome irrespective of the care they're given, with the most common type, glioblastoma multiforme, having an overall survival of only 15 months. It is hoped that the 100,000 Genomes Project will enable the identification of important genetic mutations from across the whole of the genome (in both the genome of the normal tissue and the tumour tissue), as so far it has been limited to only certain regions of the genome. Furthermore, it is hoped that the project will allow the various different types of Glioma to be better understood and so allow better tailored treatment.

Expected start date	**Q2 2017**
Expected end date	**Q2 2020**

Lead Applicant(s)	
Name	Keyoumars Ashkan
Post	**Professor of Neurosurgery**
Department	Neurosurgery
Institution	King's College Hospital
Current commercial links	Co-course coordinator for the Gliolan assisted tumour resection course run by Madec company.

Gear 2 Substudies
GL01: An exploration of ctDNA in glioma: a pilot project
GL02: Identifying new molecular sub-types and pathways of glioma
GL03: Cross-cancer analyses based on shared aetiology or molecular pathways
GL04: Identification of actionable mutations in glioma
GL05: Evolution of glioma in time and space

GL06: Non-human genomes in glioma
GL07: Determining the effects of adjuvant chemo/radiation therapy on glioma genomes
GL08: Identifying and characterising intrinsic and extrinsic mutation signatures and mutator phenotypes in glioma
GL09: New therapeutic or imaging targets
GL10: Integrating genomics and glioma clinical trials
GL11: Exceptional or highly unusual glioma cases (age, germline predisposition, excellent response, previous treatment with radiotherapy or chemotherapy, long term survivals)
GL12: Glioma cancer driver mutations in non-coding regions of the genome
GL13: Inherited variation
GL14: Functional evaluation and interpretation of potential driver mutations in glioma and follow-up analyses in additional data sets and model systems
GL15: Elderly patients with glioblastoma
GL16: Genomic and radiomic characteristics of glioma
GL17: Predictive genomic biomarkers of transformation imaging phenotypes
GL18: Genomic biomarkers of pseudoprogression

GeCIP domain - Expression of interest

Full proposal

Title *(max 150 characters)*	**Glioma cancer research in the 100,000 Genomes Project**

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

We propose to sequence Tumour/Normal pairs from 1,000 patients with adult glioma. The prospective collection of samples takes advantage of the shared location of neurosurgery and GMCs. We are cognisant of international efforts in sequencing, including TCGA project. Our collective view is that an "all-comers" approach will not maximize the potential of the GeL project and we will therefore liaise with GMCs to guide collection towards the most biologically and clinically relevant samples. These include trial patient samples, non-GBM glioma and rare subtypes and Tumour/Normal pairs across different clinical phenotypes (rapid progression v stable disease v remission).
Sampling bias is important therefore we shall seek to collect multiple samples. We will also assess tumour-specific features such as the need for microdissection, desirability of additional sequencing depth for selected samples, and deviations from a standard analysis pipeline
(1) Somatic driver gene identification will rely on statistical methods of assessing mutation over-representation in genes and pathways, such as MutSigCV. We will work with other GeCIP Domains to develop methods of assessment for mutations in non-coding regions. (2) Complementary analyses: Further analyses of DNA (outside genome sequencing), RNA and protein studies (including immunohistochemistry), and the use of model systems and bespoke in silico assessments all have several potential uses downstream of the genome sequencing. For example, it may inform functional annotation, provide actionable targets (e.g. pathway-based), and allow more sensitive driver identification (e.g. CNVs, structural variants). (3) New classifiers: Integrated analysis and machine learning methods will be used to identify new classifiers of glioma based on molecular features, histology and patient characteristics. Refined genetic pathways will also be determined. These classifiers will be tested as predictors of features such as prognosis and response to treatment in the GeL data sets and validated in collaborators' samples. (4) Cross-cutting analysis: We anticipate in extensive cross-GeL collaborations, including both cross-cutting and disease-specific themes. Examples include inherited cancer, population genetics, and other cancer types. We shall play an active role in cross-cancer analyses (e.g. pan-cancer drivers, method comparisons, new analytical tools, collaboration with inherited cancers GeCIP) and pan-GeL analyses (e.g. incidental findings). (5) Specific focus areas: We plan that the Domain will undertake a number of specific projects on glioma subtypes, each run by small groups of individuals with special interests, supplemented where necessary by researchers and clinicians outside the Domain. These will be added to as time elapses and will require specific funding which may be obtained by the Domain or with the Domain's support from UK and international funders. Examples include: Molecular genetic analysis of tumour margins; Unusual glioma morphologies, e.g. cancers with highly divergent cellular architecture; Cancer evolution in space and/or time, or as a result of treatment; Improving the utility of ongoing clinical trials (e.g. GALA-BIDD, PARAQDIGM); Molecular staging and optimal biopsy analysis; Non-human genomes in gliomas; High mutation burden cancers; Exceptional treatment responders such as immunotherapy.

Collaborations including with other GeCIPs. *Outline your major planned academic, healthcare, patient and industrial collaborations. This should include collaborations and data sharing with other GeCIPs. Please attach letters of support.*

Role	Experience

Domain leads Keyoumars Ashkan k.ashkan@nhs.net	Keyoumars Ashkan is a professor of Neurosurgery specializing in neuro-oncology who has led the neuro-oncology service worked in King's College Hospital, the largest in the UK, for over 8 years. He is an expert in clinical management of patients with brain tumours as well as clinical trials for novel therapies. The nationally published data has demonstrated that the brain tumour patients treated in his service have the best 1 year survival in the UK. He works closely with brain tumour research charities and is a member of neuro-oncology James Lind Alliance
Domain deputy Richard Houlston Richard.houlston@icr.ac.uk	Richard Houlston is professor in molecular and population genetics at The Institute of Cancer Research and Hon. Consultant Physician at the Royal Marsden Hospital's NHS Trust. He has led a number of initiatives in the identification of susceptibility genes for glioma and genes significantly mutated in tumours. These analyses have been complemented by examination of the relationship between germline and tumour profile and their impact on patient outcome.
GMC representative Colin Watts	He holds a University of Cambridge Clinical Senior Lecturer & Honorary Consultant Neurosurgeon . He is Chair International Rare Cancers Initiative for Brain (2013 -), Neuro-Oncology Faculty EANS (2012-), Neuro-Oncology Faculty WFNS (2012 -), Chairman NCRI Clinical Trials Group, Brain Tumours (2011-), Director of Studies (Clinical) Peterhouse (2010-), Committee member NCRI Clinical Trials Group, Brain Tumours (2008), Chair NCRI technology sub-group, Brain Tumours (2009 – 12)100 He is new Chair of the European Association of Neurosurgical Societies (EANS) tumour section through which this GeCIp will be able to establish a comprehensive tissue sampling programme through international collaborations.
Patient representative Helen Bulbeck	Dr Helen Bulbeck is Director of services and policy at the brainstrust - the brain cancer people. This is a UK based brain cancer charity, dedicated to improving clinical care for brain tumour sufferers and providing co-ordinated support in their search for treatment. The trust provides support and advice at the point of diagnosis and beyond, by updating treatment, improving care and, ultimately, saving lives.
Education and Training lead Daniel Walsh	Daniel Walsh holds a consultant neurosurgical post at Kings College, London. He currently chairs the department Morbidity and Mortality meeting at the department of neurosurgery, King's College Hospital. He is departmental lead for surgical training and is a member of the South Thames Neurosurgical Training Committee.
Validation and Feedback representative Safa Al-Sarraj	Safa Al-Sarraj is the professor of neuropathology at King's College Hospital, specialising in brain tumours. He is a core member of the adult and paediatric neuro-oncology MDTs and regularly provides second opinions nationally for challenging tumours. He is a leading figure in the UK in introduction of modern molecular diagnosis for brain tumours and its integration with the pathological diagnosis.
Other domain members	Michael Jenkinson (The Walton Centre, Liverpool): Neurosurgery, neuro-imaging Susan Short (Leeds University): Neuro-oncology, clinical trials (adjuvant setting) and translational medicine, radio-chemotherapy Anthony Carr (MRC DNA damage Centre, Sussex University): Functional studies of DNA damage Andrea Sottoriva (ICR): Cancer evolution, bioinformatics, systems medicine Anthony Chalmers (Glasgow University): Neuro-oncology, clinical trials and translational medicine radiosensitivity, tumour micro-environmental analyses, in vitro studies Thomas Booth (Kings College): Neuro-radiology, diagnostics Paul Grundy (Southampton University): Neurosurgery Pietro D'Urso (Manchester): Neurosurgery

	James Laban (St. Georges Hospital Medical School): Neurosurgery
Potential international collaborators	Professor Marc Sanson (CRICM, Paris, France) Professor Konstantinos Polyzoidis (University of Thessalonki, Greece) Professor Matthias Simon (University of Bonn, Germany) Professor Alfredo Quinones-Hinojosa (John Hopkin's, USA) Professor Mark Lathrop (Genome Quebec, McGill University, Canada)

The Domain membership, in particular the neurosurgeons, oncologists and neuropathologists, have well established collaborations with industrial partners and hence have early access to an active pipeline of novel agents. Researchers at the ICR through links with the CR-UK Centre for Drug discovery are particularly well placed to exploit GeCIP discoveries. The team at King's College Hospital have extensive experience with novel immunotherapeutic agents for brain tumours in close collaboration with the industry. Other Domain members have active partnerships with the Biotech. industry including companies working in the field of high-throughput sequencing and translational genetic/molecular diagnostics.

Detailed research plan – Cancer Main Programme Gear 2 studies

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL01: An exploration of ctDNA in glioma: a pilot project**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Any glioma
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Single cancer sample and sample for plasma DNA extraction; further cancer sample for additional 'omics analysis would be very helpful
# cores per tumour (if multi-region biopsying proposed)	N/A
Follow-up samples following first ascertainment	Plasma post-treatment and then up to 3-monthly for monitoring, and relapse cancer sample if available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To investigate the prevalence, levels and utility of circulating tumour DNA Circulating tumour cells may optionally also be analysed.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	For glioma, relatively little is known about ctDNA burden. We shall investigate this by collecting multiple samples for ctDNA extraction from a set of about 30 patients at diagnosis, post-surgery and on follow-up. Mutations in the primary cancer will be used as targets to assess the ctDNA. Based on these findings, we shall design further experiments.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	None
Is this sub-study a new therapeutic trial?	N/A

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL02: Identifying new molecular sub-types and pathways of glioma**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Any glioma
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)	All available

It is assumed that in addition there will be one germline sample per patient.	
# cores per tumour (if multi-region biopsying proposed)	N/A
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To identify molecular groups of glioma based on unsupervised cluster analyses and machine learning
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Although most of the major driver genes for glioma are likely to have been found by groups such as TCGA, rare or weak-effect "mini-driver" mutations in coding regions may remain to be found, and we shall search assiduously for these. However, a more fruitful task may be to refine the current molecular classification of glioma. Ideally, this would be based on multi-omic (poly-omic?) approaches that can be used should funding be available. Initially, working with the Machine Learning domain, we shall search for new mutation-based groupings beyond the triad of hypermutation, ultramutation and chromosomal instability – and arguably CpG island methylation – that currently holds. A variety of tools will be used including both conventional hierarchical and Kmeans clustering and principal component analysis, and specialist Bayesian methods (e.g. regression, network analysis). The molecular pathways (small mutations, copy number changes, etc) underlying these cancer groups will be identified and validated in independent data sets. Associations with clinico-pathological variables, such as survival, will be assessed in clinical trial data sets.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	Yes. Validation and testing for associations with clinicopathological variables only. No.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL03: Cross-cancer analyses based on shared aetiology or molecular pathways**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-	Any glioma

type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Single sample from each cancer
# cores per tumour (if multi-region biopsying proposed)	N/A
Follow-up samples following first ascertainment	None
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To examine genomic similarities and differences between pairs of cancers with shared aetiology and/or molecular features
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Many cancers share genetic and other features, and TCGA and others have identified a number of driver genes mutated in more than one cancer type (sometimes referred to inaccurately as "pan-cancer drivers". Many of the analyses detailed elsewhere for glioma will be performed across these cancer types. Exemplar questions of note include whether shared driver mutations tend to occur at similar stage of carcinogenesis, whether there are alternative means of (in)activation of the same pathway in different tissue types, and whether clinicopathological-molecular associations hold across cancers..
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL04: Identification of actionable mutations in glioma**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Any glioma
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Single sample from each cancer
# cores per tumour (if multi-region biopsying	N/A

proposed)	
Follow-up samples following first ascertainment	None
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To identify mutations that may influence therapy, and/or are predictive of prognosis
Scientific case and insights that will be gained from this cohort (more details, as indicated)	We shall identify mutations and forms of genomic instability that have potential relevance for patient management. We shall work with Validation and Feedback to provide expertise in this regard. We shall assess selected variants of uncertain pathological significance using more extensive bionformatic assessments and wet lab - functional assays.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL05: Evolution of glioma in time and space**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Specific and selected patients from whom several distinct cancer samples can be obtained, to include (i) multiple sites samples from the primary tumour and (ii) samples at different times (to include before and after therapy, at presentation, relapse or death, etc)
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	These will all have to be decided on a case-by-case basis, but envisaged to be 3 from primary. It is important to note that we may wish some samples to be sequenced at greater than the standard depth (e.g. double-sequenced) to provide enough power for sub-clonal analyses.
# cores per tumour (if multi-region biopsying proposed)	
Follow-up samples following first ascertainment	
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To determine how gliomas evolve in different natural or artificial environments To identify sub-clonal and spatial driver mutations and copy number changes To examine heterogeneous treatment resistance mechanisms
Scientific case and insights that will be gained from this cohort (more details, as indicated)	A burst of NGS-based studies has transformed cancer evolution analysis from a backwater to mainstream as a result of the excitement it has

	engendered in the Oncology community. Much remains to be done, however. In part this will consist of more detailed understanding of tumorigenesis in time and space, especially as regards mechanisms of resistance to targeted, genotoxic and immunotherapies, and linking the findings into therapeutic strategies and prognostic markers. Our overall strategy in the short term is to continue to describe the evolution of glioma at the highest possible level of complexity within the GeL project. We wish to use cutting edge statistical methods to identify sub-clones within biopsies, to correct for copy number and tumour cell fraction, to integrate copy number changes into evolutionary trees, to time mutation events, to detect bottlenecks and selection, to relate mutations to microenvironment and examine germline influences on invasion and metastasis. Gradually, we will move to validation studies and hypothesis generation/testing outside GeL.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	Yes, for a subgroup of patients: Gala Bidd trial looks at the neuropathological characteristics of fluorescing areas of gliomas versus areas which do not for those tumours undergoing florescent guided resection. The current proposal can be extended to look at the genomics differences too. No, for other subgroup of patients although they would be excellent candidates. We expect that these studies will be restricted to GMCs in which there exist neuropathologists with special interests in these analyses (or where there is access to the necessary surgical equipment in the case of fluorescence guided resection).
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL06: Non-human genomes in glioma**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	All patients
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one*	Single sample

germline sample per patient.	
# cores per tumour (if multi-region biopsying proposed)	N/A
Follow-up samples following first ascertainment	None
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To identify the presence of non-human genomes within gliomas and relate that to molecular biology
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Cancer genomes are known to contain viral genomes of uncertain significance. In glioma, for example, HS virus has long been mooted as a causal agent. We shall search for non-human DNA integrated into the cancer DNA. If necessary, we shall work with cross-cutting domains with expertise in this area. We envisage that the non-human genes could be expressed or act as mutagens.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL07: Determining the effects of adjuvant chemo/radiation therapy on glioma genomes**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	All cancers treated with adjuvant therapy (within or outside clinical trials) from which pre-treatment sample and post-treatment sample are available
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Biopsies/ resection (pre-adjuvant therapy)
# cores per tumour (if multi-region biopsying proposed)	Variable
Follow-up samples following first ascertainment	Post-adjuvant treatment biopsy/ resection (samples may require sequencing at additional depth).
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To determine the effects of adjuvant therapies on cancer genomes, including their evolution, the identification of resistance (epi)mutations and the identification of post-therapy driver mutations, all in relation to therapeutic response. Non-genetic factors with influences

	on resistance (stem cell fraction, hypoxia, immune/inflammatory response) will also be assessed via RNA.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Surgical resection followed by adjuvant chemo-radiation therapy is now the standard of car for high grade gliomas (and also in specific cohort of patients with lower grade gliomas). It is known that adjuvant therapy can produce profound responses in some patients (eg glioblastoma patients with MGMT methylation), with a spectrum from good response to progression in others. A proportion of patients with tumour progression after adjuvant therapy may undergo repeat surgical excision of the recurrent tumour. The variation in response to adjuvant therapy strongly suggests that a better understanding of how adjuvant therapy works has the potential to improve patient selection and ultimately the therapy itself. This is likely to be increasing important for recent technical advances, whether in radiotherapy delivery or in new agents. For example, are the cancer cells remaining after radiotherapy unscathed by treatment, or are they grossly mutated or chromosomally rearranged? The choice of secondary therapies would depend greatly on answering such questions.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL08: Identifying and characterising intrinsic and extrinsic mutation signatures and mutator phenotypes in glioma**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	All patients
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one*	All available

germline sample per patient.	
# cores per tumour (if multi-region biopsying proposed)	All available
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To perform a deep analysis of somatic mutations, including differences in: gross features (e.g. copy number v SNV); burden/spectrum (e.g. in relation to DNA repair defects or specific environmental aetiologies); signatures; locations with respect to chromatin features (transcribed regions, open chromatin, late/early-replicating, cohesin binding, etc); their timing during carcinogenesis; driver mutation spectra and selective consequences; underlying genomic instability; clonal structure; DNA modifications (e.g. methylation, atypical bases); replication (origins, strand, use of lesion bypass error-prone polymerases); and several other features. To examine whether any mutations are present in tumour stroma (including clonal TCR rearrangements, etc) To relate the findings to cancer behaviour and aetiology
Scientific case and insights that will be gained from this cohort (more details, as indicated)	The factors contributing to a cancer's mutation burden and spectrum are potentially many. Using the exceptionally large, high quality data set afforded by GeL, we shall perform a deep analysis as outlined above, with the ultimate aim of explaining all the mutations found in each tumour.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL09: New therapeutic or imaging targets**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	All patients
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)	All available

It is assumed that in addition there will be one germline sample per patient.	
# cores per tumour (if multi-region biopsying proposed)	All available
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To identify mutations that could provide new targets for therapy, prevention or imaging
Scientific case and insights that will be gained from this cohort (more details, as indicated)	This work is largely implicit within other projects, and will presumably be a focus of commercial organisations accessing the GeL data. We will work with these organisations to annotate data and identify the targets with the most potential for clinical use.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL10: Integrating genomics and glioma clinical trials**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Tumours yielding sufficient DNA for sequencing of genomes
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Primary, optionally with additional samples
# cores per tumour (if multi-region biopsying proposed)	Generally one, but may be more than one for a sub-group of patients
Follow-up samples following first ascertainment	Generally <2
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To determine how cancer evolve in response to the therapies used within trials, to define molecular sub-types (in part for choice of therapy) and to identify actionable mutations
Scientific case and insights that will be gained from this cohort (more details, as indicated)	We shall integrate genetic information with data from clinical trials performed during the time course of the GEL initiative.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study?	Anticipated after obtaining regulatory approval. There are a number of novel commercial (eg

Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	DCVAX) and non commercial trials (EORTC) currently active in the UK which will be candidates for this alignment
Is this sub-study a new therapeutic trial?	It may result in a trial amendment. It is possible that data from GeL will be used to allocate patients to treatment arms or to bespoke treatment.

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL11: Exceptional or highly unusual glioma cases (age, germline predisposition, excellent response, previous treatment with radiotherapy or chemotherapy, long term survivals)**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	We may request enrichment for these cancer types, where ascertainment and GeL recruitment are feasible.
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	As many as available
# cores per tumour (if multi-region biopsying proposed)	To be decided
Follow-up samples following first ascertainment	Recurrences
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To identify mutations and other molecular features specific to these classes of patient
Scientific case and insights that will be gained from this cohort (more details, as indicated)	We shall examine these specific groups of patients for unusual features, mostly in a hypothesis-driven fashion. For example, do exceptional responders to a particular targeted therapy have unusual mutations in the target genes, do the genomes of very young patients (<30 years) indicate a cryptic Mendelian predisposition.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL12: Glioma cancer driver mutations in non-coding regions of the genome**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	All patients
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	All available
# cores per tumour (if multi-region biopsying proposed)	All available
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To identify and characterise non-coding mutations that drive tumorigenesis
Scientific case and insights that will be gained from this cohort (more details, as indicated)	It is likely that enrichment for specific features will be required, rather than an agnostic global analysis, focussing on features with an elevated prior risk of functionality, including the following: Copy number - recurrent or focal changes Translocations/fusion genes/inversions (may be coding but included for completeness) Non-coding RNA Promoter and UTRs, e.g.miRNA binding sites Regulatory regions, e.g. binding of specific transcription factors Conserved regions Open chromatin Reactivated pseudogenes Regions around known cancer driver genes Multiple strands of evidence are likely to be needed to demonstrate driver status and statistical methods must be adapted to this. Set-based or burden tests may be required owing to high levels of genetic heterogeneity. Some work will be hypothesis driven, e.g. EGFR-pathway modulation by mutations affecting binding of glioma-specific transcription factors
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL13: Inherited variation**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	All patients
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	All available
# cores per tumour (if multi-region biopsying proposed)	All available
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To identify germline factors that are important for glioma oncogenesis
Scientific case and insights that will be gained from this cohort (more details, as indicated)	The genomes sequenced from the constitutional DNA sample will be useful for assessing inherited influences on (i) susceptibility (in concert with the InCaP domain familial cancer) (ii) cancer features such as grade, etc (iii) prognosis, response to therapy and toxicity (iv) somatic mutation burden, spectrum, etc (v) anti-cancer immune response (vi) driver mutations and (epi)genetic pathways In addition, we will identify undetected Mendelian mutations, perhaps including some mosaics derived from the sequencing of the tumour. These findings are likely to be reported back to many participants via the Validation and Feedback domain, although in difficult cases these may require functional assessment which we will undertake if feasible.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL14: Functional evaluation and interpretation of potential driver mutations in glioma and**

	follow-up analyses in additional data sets and model systems
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	N/A
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	N/A
# cores per tumour (if multi-region biopsying proposed)	N/A
Follow-up samples following first ascertainment	N/A
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To perform functional assessment of and follow up selected findings in additional data sets and model systems
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Certain variants that we detect will require (i) validation/replication in additional data sets. (ii) functional effect assessment using multiple approaches including laboratory analysis, and (iii) further studies in cell, organoid and animal models (for example to elucidate pathogenic mechanisms, epistasis, pleiotropy and co-evolution). The GeCIP domain already includes individuals with expertise in many of the key areas but shall recruit additional functional biologists as the programme progresses. We believe that a computational approach to variant effect prediction is essential and there already exist excellent tools and databases for this purpose. However, such as approach is limited – not least because the specific functions that need to be deranged to cause cancer are unknown for many mutated genes. We also know that many mutations are cancer type and allele-specific, and we have computational skills and the specific laboratory expertise to perform the necessary assessments for glioma oncogenesis.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	No
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL15: Elderly patients with glioblastoma**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Age ≥70 Histologically confirmed diagnosis of glioblastoma
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Biopsy or tumour resection specimen from initial diagnostic or therapeutic neurosurgical intervention. FF plus FFPE required
# cores per tumour (if multi-region biopsying proposed)	All available
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	- investigate why elderly GBM patients have such a dismal prognosis, even when treated with radical multimodal therapy - identify WGS signatures that correlate with survival outcomes, and how these relate to treatment modality - identify WGS signatures that correlate with MGMT methylation status in elderly GBM, and how these relate to outcomes after treatment with radiotherapy and/or chemotherapy
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Glioblastoma in the elderly has particularly dismal prognosis and the reasons for this are not well understood. Meanwhile the incidence of GBM in this population continues to rise. Elderly patients are generally under-represented in clinical trials and information on genomic and molecular biomarkers is lacking. Data from this cohort may identify novel prognostic and predictive biomarkers in this group, and may reveal novel targets for future treatments.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	Will align with HCQ (phase II, Leeds, Susan Short CI) and PARADIGM (phase I-II, Glasgow, Anthony Chalmers CI) clinical trials that are currently recruiting. Co-recruitment optional.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL16: Genomic and radiomic characteristics of glioma**

Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Gliomas at presentation
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Sample with image registration at initial presentation (biopsy or debulking surgery)
# cores per tumour (if multi-region biopsying proposed)	Multi-region sampling with image registration if possible in selected patietns.
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	At presentation, examine the WGS signatures that correlate with imaging phenotypes
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Gliomas are heterogeneous tumours whose classification is evolving with further molecular characterisation. Previous discoveries have been made with whole exome sequencing, such as that used in the TCGA, but WGS will likely yield new information. Radiomic data may reveal imaging phenotypes that correlate with genomic data which may help in the understanding of the underlying tumour biology and in the future help with diagnosis, prognosis and treatment planning.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	There is the potential to link this to other trails, including GeCIP substudies
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL17: Predictive genomic biomarkers of transformation imaging phenotypes**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Low grade gliomas at presentation
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Sample with image registration at initial presentation (biopsy or debulking surgery)
# cores per tumour (if multi-region biopsying proposed)	Multi-region sampling with image registration if possible in selected patietns.

Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	At presentation, determine the WGS predictive biomarkers of transformation imaging phenotypes
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Imaging can reveal transformation of low grade gliomas through conventional structural follow-up MR imaging. Advanced MR imaging techniques may be able to capture transformation at an earlier timepoint. This study will determine whether a genomic biomarker can predict the point of transformation on conventional structural follow-up MR imaging; and whether a genomic biomarker can predict the early point of transformation on advanced MR imaging.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	There is the potential to link this to other trails
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**GL18: Genomic biomarkers of pseudoprogression**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Glioblastoma (WHO grade IV; and MIB-1-upgraded Grade III tumors)
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites) *It is assumed that in addition there will be one germline sample per patient.*	Sample with image registration at initial presentation (biopsy or debulking surgery)
# cores per tumour (if multi-region biopsying proposed)	Multi-region sampling with image registration if possible
Follow-up samples following first ascertainment	All available
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	At presentation, determine the WGS predictive biomarkers of subsequent progression and pseudoprogression imaging phenotypes
Scientific case and insights that will be gained from this cohort (more details, as indicated)	In the last decade there has been a small increase in glioblastoma survival following improvements in chemoradiotherapy, but the new treatment has been associated with pseudoprogression, which describes false-positive progressive disease. In most clinical neuroscience centres throughout the world,

	pseudoprogression causes management dilemmas several times a week. Unlike, many other parts of the body where biopsy may be used to investigate the disease response to treatment with little associated morbidity and mortality, biopsy of an intracranial lesion requires neurosurgery with associated risks. Instead, neuroimaging is used routinely to measure treatment response but its interpretation is now limited because true disease progression and pseudoprogression cannot be distinguished. Some publications suggest that MGMT methylation status obtained at biopsy gives a priori information on whether a patient might develop pseudoprogression or not at the group level, but the data is insufficient, even at the group level, to confirm this. The key insight might be that genomic information obtained at presentation might predict a subsequent pseudoprogression imaging treatment response, informing whether an early change in glioblastoma treatment strategy is subsequently required.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study? Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	There is the potential to link this to other trails
Is this sub-study a new therapeutic trial?	No

Data and informatics requirements
All GeCIP Domains have contributed to the construction of the data model for their tumour type and have contributed to ongoing efforts within Genomics England to develop the clinical and research informatics infrastructure.

Data access and security	
GeCIP domain name	**Glioma cancer**
Project title *(max 150 characters)*	**Glioma cancer research in the 100,000 Genomes Project**

Applicable Acceptable Uses. *Tick all those relevant to the request and ensure that the justification for selecting each acceptable use is supported above.*

X *Clinical care*

X *Clinical trials feasibility*

X *Deeper phenotyping*

X *Education and training of health and public health professionals*

X *Hypothesis driven research and development in health and social care - observational*

X *Hypothesis driven research and development in health and social care - interventional*

X *Interpretation and validation of the Genomics England Knowledge Base*

X *Non hypothesis driven R&D - health*

X *Non hypothesis driven R&D - non health*

X *Other health use - clinical audit*

X *Public health purposes*

X *Tool evaluation and improvement*

Information Governance

X The lead for each domain will be responsible for validating and assuring the identity of the researchers. The lead may be required to support assurance and audit activities by Genomics England.

Any research requiring access to the embassy will be required to complete IG Training and read and sign a declaration form. Access will only be granted once these requirements have been met.