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	**Melanoma cancer**
Project title *(max 150 characters)*	**Melanoma cancer research in the 100,000 Genomes Project**

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

a. Discovery of oncogenic drivers of melanoma. In the case of rare melanomas such as uveal melanoma, the drivers are yet to be identified.
b. Informing tumour heterogeneity and contribution of clonal evolution to metastases and drug resistance in melanoma. These analyses will reveal variants that are relevant to the process of metastases and therapeutic resistance and will present important opportunities to identify prognostic and predictive biomarkers.
c. Use the melanoma genome datasets to define the neoantigenic landscape of human melanoma, its association with disease progression and patient survival, and most importantly, to define the most relevant immune-regulatory pathways controlling the fate and function of neo-antigen reactive T cells in vivo.
d. Cell-free tumour DNA in melanoma and its correlation with tumour genomic profiles. We will also explore whether mutations detected in tumour-free DNA can predict disease relapse and inform the mechanisms of treatment resistance.

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)*

Melanoma is caused by uncontrolled cell growth of certain cells in the skin, and are primarily the result of exposure to high levels of ultraviolet light i.e. from spending too long in the sun, or from excessive use of tanning devices.
There are ~12,000 new cases and ~2,200 deaths from melanoma each year in the UK, but new targeted therapies have significantly improved outcomes in melanoma. There has been particular progress in understanding how drugs that work with the immune system can be used to fight and overcome melanoma. However, how well those drugs work vary between individuals and it's likely that the reasons behind this are due to the variety in people's genes. Therefore the Melanoma GeCIP domain will be using the genetic sequence from the 100,000 Genomes Project to understand what those variations are and how they can be used to identify which patients will and won't benefit from certain medication.
The impressive advances in melanoma care has increased average survival in patients with advanced disease from 9 months (2010) to 25-30 months (2015), but most advanced patients will still die from their disease. Improved understanding of melanoma genetics is needed to improve outcome for melanoma patients.

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

Lead Applicant(s)	
Name	Professor Paul Lorigan
Post	Professor of Medical Oncology and Honorary Consultant Medical Oncologist

Department	
Institution	Christie NHS Foundation Trust
Current commercial links	

Deputy Lead Applicant(s)	
Name	Dr James Larkin
Post	Consultant Medical Oncologist
Department	
Institution	Royal Marsden Hospital
Current commercial links	

Gear 2 Substudy leads		
Name	**Gear 2 Substudy**	**Institution**
Adams, Turajilic, Lorigan, Corrie, Larkin, Marais, Middleton	ML01: Genomic evolution of melanoma brain metastases	
Larkin, Corrie, Middleton, Paul, Turajilic, Marais, Sergio Quazeda, Zelenay, Miller	ML02: Molecular determinants of response to immunotherapy treatments	
Lorigan, Larkin, Turajilic, Marais, Dohmen	ML03: Molecular characterisation of patient with mucosal melanoma	
Marais, Springer, Larkin, Turajilic, Dohmen, Lorigan	ML04: Novel pan RAF inhibitors as a way to circumvent resistance to BRAF targeted therapy in metastatic melanoma	
Coupland, Sacco, Kalirai, Coulson, Heinmann	ML05: Mutational burden and heterogeneity in uveal melanoma (um)	

GeCIP domain - Expression of interest

Full proposal	
Title *(max 150 characters)*	**Melanoma 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.*

The domain has previously demonstrated the benefits of integrating this type of data with clinical annotation. We recognise that the ability to correlate mutations in loci outside regions targeted by exon-capture opens exciting possibilities, particularly in the context of for example noncoding expression, where many novel loci have yet to be identified. Combined with RNA sequencing data and precise clinical annotation in a large cohort, the potential benefits are tremendous.

Broadly, we wish to explore:

a) Discovery of oncogenic drivers of melanoma. Whilst around half of melanomas are driven by oncogenic mutations within the RAS/RAF/MEK/ERK MAPK pathway, the underlying drivers of remaining cases are often difficult to identify. To date, the largest cohort of cutaneous melanomas profiled (TCGA) includes only ~200 cases, and profiling was done by WES rather than WGS. In the case of rare melanomas such as uveal melanoma, the drivers are yet to be identified.

b) Informing tumour heterogeneity and contribution of clonal evolution to metastases and drug resistance in melanoma. Significant genetic diversity between primary and metastatic lesions has been identified in solid tumours, including melanoma. However, resistance is also driven by a number of other, non-genetic factors, with phenotypic shifting and upregulation of resistance factors, some due to epigenetic modifications. By profiling matched samples (for example responding and progressing lesions) we will identify the subclones which expand over time during disease progression as a function of their fitness (determined by the subclonal driver) and extrinsic pressures (including therapy and microenvironment). These analyses will reveal variants that are relevant to the process of metastases and therapeutic resistance and will present important opportunities to identify prognostic and predictive biomarkers.

c) Informing mechanism of responses to immunotherapy through neoepitope prediction from WGS data. The melanoma field has led the advances in immunotherapy, and these are now showing significant benefits in a number of other tumour types. Whilst our understanding of the molecular controls of the immune system have yielded a number of very potent treatment options, the role of prognostic and predictive factors, and the importance of the tumour microenvironment and accessory cells in this process, remains poorly understood. We will use the melanoma genome datasets to define the neoantigenic landscape of human melanoma, its association with disease progression and patient survival, and most importantly, to define the most relevant immune-regulatory pathways controlling the fate and function of neo-antigen reactive T cells in vivo.

d) Cell-free tumour DNA in melanoma and its correlation with tumour genomic profiles. Tumour cell-free DNA will be isolated from plasma of tissue donors and sequenced (either targeted sequencing or next generation sequencing as routinely performed within GeCIP member institutes) to compare to tumour genomic data generated via and analysed by the GeCIP. The GeCIP will address how tumour-free DNA reflects the genomic composition of the primary and metastatic tumours, and how it can be used assess tumour burden and heterogeneity. We will also explore whether mutations detected in tumour-free DNA can predict disease relapse and inform the mechanisms of treatment resistance.

Marais, Turajlic, Newton-Bishop and Middleton have extensive experience in interrogating the genetics and epigenetics of melanoma patient samples, working in close collaboration with bioinformaticians and computation biologists including Leong, Buffa and Miller. Adams and Newton-Bishop are leads in the GenoMEL (Genetics of Melanoma) consortium. Moncrieff has experience of collaborating with The Cancer Genome Atlas Project (TCGA; NIH, USA), as the only UK site to contribute melanoma & blood samples to the project. Middleton has access to trial tumour sample sets from the national AVAST-M (n=760), DOC-MEK (n=64, wt BRAF disease) and PACMEL (still collecting, wt BRAF disease) clinical trial sets.

The GeCIP encompasses funding from all major research bodies in the United Kingdom. For example, Lorigan currently receives funding from CRUK and EUFP7 and the Christie Charity, and Larkin's funds are derived from the CTAAC, Wellcome Trust and the RMH/ICR BRC. Newton-Bishop is currently funded by CRUK, MRC, Melanoma Research Alliance, NIH, and Genetic epidemiology of melanoma (GenoMEL), Middleton is funded by departmental BRC, ECMC and CRUK grants as well as industry grants, and Marais receives funding from CRUK, the Wellcome Trust and the ERC (Investigator

Award, H2020 Award). Coupland is funded by the North West Cancer Research Programme, Fight for Sight, and MRC and Crispin Miller derives funding from the MRC, Prostate Cancer UK, and CRUK.

The GeCIP has mature mechanisms in place to assist with writing of grants to fund additional work. As outlined above, several members of the domain have programme grants funding translational studies based on integrating sequencing and multi–omics data with clinical annotation. By collaborating on data interpretation of large cohorts of samples, exciting new opportunities for translational research will form the basis of further funding proposals aimed at cancer research funding bodies such as NIHR, CTAAC, CRUK and the Wellcome Trust. Additionally, the knowledge generated by the genomics insight will inform new clinical trials and collaborations with industry partners.

Patient representatives for our domain Simon Rodwell and Mark Roberts will play a central role in how the GeCIP utilises the data generated by the 100KG programme. There will be a particular focus on developing a policy on feedback of secondary findings to patients and this will be done in close consultation with the patient representatives.
Simon Rodwell is the chief executive officer of Melanoma Focus www.melanomafocus.com , a national charity dedicated to providing a comprehensive and authoritative source of information for public and professionals alike, as well as supporting education and promoting research about melanoma.
Mark Roberts is the chief executive Challenge Cancer UK, a national charity which supports those affected by cancer. They raise funds for cancer awareness, prevention, and research. They also fundraise for patient treatment, care, and support of those affected by cancer.

The GeCIP domain includes several trainees in subjects from clinical medicine/surgery to basic research/bioinformatics. Their participation in the GeCIP will allow them to learn the challenges of next generation sequencing and its interpretation. Our clinical fellows are funded by ESMO, the Spanish Oncology Society, the Manchester Cancer Research Centre and the NIHR. Many are members of the EORTC Melanoma Group Young Investigators (YIN) Network and/or ESMO Young Oncologists, allowing sharing of teaching and research experiences.
Members of the domain are involved in several educational events targeting trainees and young oncologists including running three ESMO preceptorships, scientific committee membership of ESMO melanoma tracks 2015 and 2016, programme committee for Melanoma Focus Annual Educational Meeting 2011-15, and interacting with EORTC YIN and ESMO Young Oncologist Group. As we move towards implementation of genomics in everyday clinical practice the trainees will learn how these data can improve clinical outcomes and how to communicate the data to colleagues and patients. The bioinformatics trainees will have the opportunity to analyse large data sets with clinical annotation to identify prognostic and predictive biomarkers. The basic cancer research trainees have an unprecedented opportunity to inform their bench-work by large genomic datasets linked to patient outcome.

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.*

Domain lead Paul Lorigan	Dr Paul Lorigan is Professor of Medical Oncology and Honorary Consultant Medical Oncologist at the Christie NHS Foundation Trust. He is currently Chair of the EORTC Melanoma Group Advanced Disease Subgroup and was Chair of the NCRI Melanoma Clinical Studies Group 2006-2102. He is also Chair of Melanoma Focus, the UK charity that represents the majority of researchers and clinicians working in melanoma, funds research, provides education, updates and guidelines, advises NICE, and supports patients. With Professor Richard Marais, he leads the Manchester Melanoma Group, developing personalised medicine approaches for melanoma patients.
Domain deputy James Larkin	Dr James Larkin, Consultant Medical Oncologist at the Royal Marsden Hospital. He is a member of the NCRI Melanoma Studies Group since 2011 was chair of the Royal Marsden/Institute of Cancer Research Committee for Clinical Research from 2013-5. Since 2011 he has contributed to a number of studies that have led to the registration of new drugs for the treatment of advanced melanoma leading to 6 publications in the New England Journal of Medicine (2 as first author) and 3 in The Lancet Oncology (2 as first or senior author).
GMC representative Professor Mark Middleton, Cancer Lead, Oxford GMC	Mark Middleton's expertise is in melanoma management. His research includes the genetic and epigenetic determinants of disease progression and therapeutic resistance in BRAF wt disease – which will be his interest in the data submitted through the GeCIP. The Oxford melanoma service sees over 200 patients per year, and can access tumour and germline DNA from all disease stages. Professor Middleton has access to trial tumour sample sets from the national AVAST-M (n=760), DOC-MEK (n=64, wt BRAF disease) and PACMEL (still collecting, wt BRAF disease) clinical trial sets available exploration and validation of insights derived from the GEL programme.
Patient representative Mr Simon Rodwell, CEO Melanoma Focus	Simon Rodwell is the CEO of Melanoma Focus (www.melanomafocus.com/). He is a patient advocate with an emphasis on melanoma who champions patient recruitment into clinical trials (www.youtube.com/watch?v=sTR52WaboxQ) and de-convolutes medical terminology to simplify complex projects for a lay audience. He educates people about the dangers of excessive sun exposure with its inherent risk of melanoma and advocates the importance of early diagnosis and treatment.
Education and Training lead Dr Samra Turajlic MD	Dr Samra Turajlic is a medical oncologist specialising in the treatment of melanoma at the Royal Marsden Hospital and a CRUK Clinician Scientist at the Francis Crick Institute. Thanks to her dual role she will lead the training programme within the GeCIP for both clinicians and researchers. She has substantial experience of cancer genomics both from basic research and clinical application perspectives. She has delivered numerous lectures and teaching sessions on the topic to clinical audiences including allied health professionals.
Validation and Feedback representative Professor Richard Marais PhD	Richard Marais is the Director of the CRUK Manchester Institute and leader of the Molecular Oncology Group. He is an expert in melanoma biology and genetics and his work has provided insight into the processes that lead to the development of melanoma. He has worked on mechanisms of resistance to melanoma drugs and on the development of new second-line drugs for relapsed patients. He is currently working on implementation of precision medicine platforms for melanoma patients. He has performed extensive experience of whole exome and whole genome sequencing of melanoma samples.
Other domain members	NHS Clinicians: Paul Lorigan (Manchester), James Larkin (London), Samra Turajlic (London), Sophie Papa (London), Mark Harries (London), Paul Nathan (London), Ruth Plummer (Newcastle), Mark Middleton (Oxford), Poulam Patel (Nottingham), Julia Newton-Bishop (Leeds), Christian Ottensmeier (Southampton), Sarah Coupland (Liverpool), Marc Moncrieff (Norwich), Joe Sacco (Liverpool), Maria Marples (Leeds), Deemesh Oudit (Manchester), Katie Lacy (London) Pathology: Martin Cook (Guildford) Melanoma Genomics: Richard Marais (Manchester), Samra Turajlic (London), David Adams (Cambridge) Rare melanomas: Sarah Coupland (Liverpool), Joseph Sacco (Liverpool), Penny Lovat (Newcastle), Helen Kalirai (Liverpool) Melanoma Biology/pre-clinical models: Nathalie Dhomen (Manchester) Melanoma Biomarkers: Caroline Dive (Manchester)

	Cancer Bioinformatics: Francesca Buffa (University of Oxford), Hui Sun Leong (Manchester), Rachel Rosenthal (London), Nicolai Birkbak (London) Non-coding RNA biology: Crispin Miller (Manchester) Immunology: Christian Ottensmeier (Southampton), Sergio Quezada (London), Santiago Zelenay (Manchester) Drug Discovery: Caroline Springer (London) Trainees: Rebecca Lee (Manchester), Patricio Serra (Manchester) Sarah Valpione (Manchester), Victoria Woodcock (Oxford), Ben Fairfax (Oxford), Andrew Furness (London), Kroopa Joshi (London), Hang Xu (London), Ankit Rao (Birmingham), Lalit Pallan (Birmingham), Katy Herring (Birmingham), Stamatina Verykiou (Newcastle), Sarah Welsh (Cambridge), Hester Franks (Nottingham), Nicola Thompson (Nottingham), Victoria Woodcock (Oxford), Ben Fairfax (Oxford), Olly Donnelly (Leeds), Samantha Turnbull (Leeds) and Sally O'Shea (Leeds).
Potential international collaborators	Caroline Robert – Institut Gustave Roussy, Paris and lead for SPECTAMelSimon Furney – Cancer Genomics and Bioinformatics, Conway Institute of Biomolecular and Biomedical Research, University College Dublin
Mechanisms for Pre-competitive Interaction with Industry	Our GeCIP domain has extensive experience with developing new drugs in collaborations with the pharmaceutical and biotechnology industry. In addition to joint drug discovery programmes, the members of the GeCIP have established numerous academically-led clinical trials in melanoma in partnership with industry in the last 5 years (including PIANO, NICAM, MAXIM, AVAST-M, PACMEL, SELPAC). We are able to support our clinical trials with extensive translational research capabilities that will allow us to validate our hypothesis-driven treatment strategies in pre-clinical models, including patient derived xenografts. We possess extensive screening capabilities, so can identify combination approaches that will then allow us to approach industry to drive forward investigator-led precision clinical trials.

Detailed research plan – Cancer Main Programme Gear 2 studies

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**ML01: Genomic evolution of melanoma brain metastases**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	*Arm A).* Adults with resected locorgeional melanoma who undergo surgical resection or biopsy of melanoma brain metastases (+/- extracranial metastases) at any stage during the course of their illness *Arm B).* Adults with resected locoregional melanoma who undergo surgical resection or biopsy of extracranial metastases (without any brain involvement) at any stage during the course of their illness
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.*	*Arm A).* Primary tumour (may be single or multiple), brain metastases (single/oligometastatic disease) any extra-cranial disease (estimated 2 samples per patient) and germline sample. *Arm B).* Primary tumour, any extra-cranial disease (estimated 2 samples per patient) and germline sample.
# cores per tumour (if multi-region biopsying proposed)	Single core per tumour
Follow-up samples following first ascertainment	If any patients from *Arm A* go on to have intra or extracranial relapsed disease resected as part of routine clinical care this should also be collected.
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	To study whether there exist distinct molecular features distinguishing those patients who develop single/oligometastatic (≤4) brain metastases from those who develop more widespread intracranial and concurrent extra-cranial disease and whether these may be exploited for early detection and/or treatment.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Melanoma has the highest propensity to metastasise to brain and the prognosis for these patients remains extremely poor. Broad profiling studies in other solid cancers have shown that metastases to the brain have distinct molecular features when compared to other extracranial sites and there is evidence that the central nervous system might have its own “brain-specific” evolutionary branching. Patients who develop single/oligometastatic intracranial disease can often be treated with locoregional tumour-directed therapies (including neurosurgery/stereotactic radiosurgery) and their outlook is generally

	better. Defining the molecular evolutionary trajectory of primary melanoma and its spread to the brain compared with distant extracranial disease and correlating with clinicopathologic information will provide a unique understanding of the pathogenesis of what is frequently the final common pathway for patients dying of melanoma and a major cause of disease-related morbidity.
Is this sub-study dependent on a particular turnaround-time for sample→clinical result? State necessary TAT	No immediate clinical applications Could help inform the alignment of patients to appropriate phase I clinical trials
Is this sub-study dependent on using diagnostic biopsy material?	At diagnosis: Primary tumour only Post diagnosis: Extra-cranial metastatic tissue (if available)
Is follow-up with ctDNA important/essential in this cohort?	If plasma is available for these patients at time of tissue biopsy, ctDNA analysis would be valuable
Is any other type of molecular analysis of the tumour proposed as part of study of this (e.g. RNA- seq, methylation analysis)?	RNA-seq analyses will be conducted on all tumour samples
Numbers of WGS proposed and recruitment projection	
How many patients do you plan to recruit in total to this cohort? How many WGS would it be proposed were used on this cohort?	*Arm A).* 50 patients, 150 whole genomes *Arm B).* 100 patients, 300 whole genomes
How many patients meeting this cohort eligibility present in England per year?	*Arm A).* ~800 patients *Arm B).* ~1000 patients
What number of patients of this cohort eligibility do you anticipate recruiting to 100KGP per year (factoring in non-consent, failure to obtain appropriate samples, technical failure of samples)?	*Arm A).* ~25 patients *Arm B).* ~10 patients (samples will also come from other melanoma studies also submitted)
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?	MelResist (local translational study) AVAST-M (national phase III CRUK funded adjuvant trial, patients on follow-up lifelong) Co-recruitment is not mandatory
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	ML02: Molecular determinants of response to immunotherapy treatments
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical	Metastatic patients undergoing treatment with novel immunotherapy agents, combinations or

characteristics, epidemiological characteristics)	sequences in early phase clinical trials.
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.*	metastatic disease prior to entry on trial
# cores per tumour (if multi-region biopsying proposed)	2
Follow-up samples following first ascertainment	Either 1 responding site and/or one progressing site
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	Immunotherapy has revolutionised the treatment of melanoma, extending the median survival by > 3 fold and with some patients going on to be long term survivors. However not all patients benefit and some patients appear to get a mixed response, with response in one area and progression elsewhere. The understanding of the molecular determinants of response to immunotherapy is evolving rapidly. They key role of neoantigen profile, clonal neoantigen burden, tumour microenvironment and signaling pathways are increasingly appreciated. Strategies to improve responses and to 'convert' non responders to responders include the use of combination immunotherapy with checkpoint inhibitors, vaccines, novel schedules etc. are being explored by a number of early phase trials in our institutions. Many of these studies are just about to start and so the timing is perfect. The plan is to link WGS or responding /progressing lesions to other investigations (cfDNA, RNAseq etc.) in a number of early phase and more advanced trials, and to routine clinical practice for mixed responses. WE will harness the power of the Melanoma Network in the UK, incorporating ECMC centres carrying out early phase trials, and the larger network of NCRI Centres to recruit patients with mixed responses to licensed treatments, to address these critically important challenges. The proposal brings together the majority of the major researchers in this field, and will reach out to others not already committed.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Determinants or response and resistance to novel immunotherapy treatments, building on the work already ongoing in the individual groups, linking the UK expertise in a coordinated way to allow access to valuable samples

Is this sub-study dependent on a particular turnaround-time for sample→clinical result? State necessary TAT	No
Is this sub-study dependent on using diagnostic biopsy material?	At diagnosis: No Post diagnosis: Yes
Is follow-up with ctDNA important/essential in this cohort?	Not essential but very important and will be collected in many centres.
Is any other type of molecular analysis of the tumour proposed as part of study of this (e.g. RNA- seq, methylation analysis)?	Please see above. All of these
Numbers of WGS proposed and recruitment projection	
How many patients do you plan to recruit in total to this cohort? How many WGS would it be proposed were used on this cohort?	80-100 patients and 400-500 WGS
How many patients meeting this cohort eligibility present in England per year?	Many patients, the main issue limitation is linking to treatment with novel agents and schedules
What number of patients of this cohort eligibility do you anticipate recruiting to 100KGP per year (factoring in non-consent, failure to obtain appropriate samples, technical failure of samples)?	50%
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?	This will be linked to a number of studies that are in set up or approved. These include Immunocore IMCgp201 Phase 1/2 study, BMS 511 and 401, EORTC Phase 2 Trial and investigator led studies at RMH and Christie Hospital.
Is this sub-study a new therapeutic trial?	These are investigator led proposals.

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**ML03: Molecular characterisation of patient with mucosal melanoma**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	First line locally advanced or metastatic mucosal melanoma 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.*	1 at first presentation of locally advanced or metastatic
# cores per tumour (if multi-region biopsying proposed)	2
Follow-up samples following first ascertainment	1
Purpose of analysis WGS and clinical data from	Mucosal melanoma is a rare subtype of

this cohort of patients (brief)	melanoma. Approximately 10-15% of patients have an activating mutation in CKIT and are eligible for PIANO, a CRUK funded study of a new CKIT inhibitor PLX3397. The majority of patient screened for the trial will not be eligible. Many will have a biopsy as part of the screening. Treatment options for these patients are poor and response to immunotherapy is poorer than for cutaneous melanoma, due in part to the lower mutational burden. We plan to look in depth at the CKIT wild type patients for who there are few treatment options, looking for targetable mutations, neoantigen expression and other disease modifying features. These studies will be linked to other studies where fresh material can be accessed quickly, to establish patient derived xenografts, CDX, drug screens, cfDNA etc.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	WGS data will be correlated with response to various treatments in the CKIT wild type patients. Repeat biopsy will be carried out in consenting patients progressing on treatment. We have preliminary data supporting contribution of a mixed clonal population to the clinical behaviour in one such patient and identified a novel drug target in this patient.
Is this sub-study dependent on a particular turnaround-time for sample→clinical result? State necessary TAT	No
Is this sub-study dependent on using diagnostic biopsy material?	At diagnosis: No Post diagnosis: Yes
Is follow-up with ctDNA important/essential in this cohort?	Yes -6/8 samples per patient, taken every month
Is any other type of molecular analysis of the tumour proposed as part of study of this (e.g. RNA- seq, methylation analysis)?	A subset of patients in the main PIANO centres will have more in-depth analysis done including PDX, CDX, proteomics, metabolomics etc.
Numbers of WGS proposed and recruitment projection	
How many patients do you plan to recruit in total to this cohort? How many WGS would it be proposed were used on this cohort?	20-30
How many patients meeting this cohort eligibility present in England per year?	200
What number of patients of this cohort eligibility do you anticipate recruiting to 100KGP per year (factoring in non-consent, failure to obtain appropriate samples, technical failure of samples)?	10-20%
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study?	Phase 2 Study PIANO. This will be a sub-study inpatients not eligible for PIANO

Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	
Is this sub-study a new therapeutic trial?	Piano Study is open and recruiting in 10 UK centres

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**ML04: Novel pan RAF inhibitors as a way to circumvent resistance to BRAF targeted therapy in metastatic melanoma**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Approximately 50% of patients with metastatic melanoma have an activating mutation in BRAF which drives proliferation through the MAPK pathway. Selective BRAF inhibitors have been a huge advance in the treatment of advanced melanoma and have transformed outcomes for eligible patients. Newer strategies including vertical blockade of the pathway have resulted in more patients responding for longer. However acquired resistance still occurs in the majority of patients after a median of approximately 12 months. Blocking the pathway more broadly has been shown to be of benefit in preclinical models. This group is developing pan RAF inhibitors and has a candidate agent in early phase clinical trial. In addition, we have a large number of paired samples of patients before and after resistance has developed, and have a number of patient derived xenografts that we are treating in parallel to the patient treatment. This group is recognised internationally as leading the research in this area.
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.*	15
# cores per tumour (if multi-region biopsying proposed)	2
Follow-up samples following first ascertainment	10
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	These data will be linked to cfDNA studies, metabolomics, cell lines, cfDNA in patients responding to and becoming resistant to pan RAF inhibitors
Scientific case and insights that will be gained from this cohort (more details, as indicated)	There are at least eight known mechanisms of resistance to BRAF inhibitors, either due to

	reactivation of the MAPK pathway or other pathways. PAN RAF inhibitors are aimed at addressing many of these. The WGS will be linked with other detailed studies already ongoing (see above) to elucidate mechanisms of response and resistance in eligible patients being treated with new candidate molecules in academic led studies.
Is this sub-study dependent on a particular turnaround-time for sample→clinical result? State necessary TAT	No
Is this sub-study dependent on using diagnostic biopsy material?	At diagnosis: No Post diagnosis: yes
Is follow-up with ctDNA important/essential in this cohort?	Yes
Is any other type of molecular analysis of the tumour proposed as part of study of this (e.g. RNA- seq, methylation analysis)?	Yes, please see above
Numbers of WGS proposed and recruitment projection	
How many patients do you plan to recruit in total to this cohort? How many WGS would it be proposed were used on this cohort?	15
How many patients meeting this cohort eligibility present in England per year?	800-1000
What number of patients of this cohort eligibility do you anticipate recruiting to 100KGP per year (factoring in non-consent, failure to obtain appropriate samples, technical failure of samples)?	Recruiting to Phase 2 study
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?	Phase II study of novel Pan Raf Study funded by Welcome Trust, Royal Marsden Hospital and Christie Charity. Study is being carried out at RMH and Christie Hospitals.
Is this sub-study a new therapeutic trial?	Yes. Please see above

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**ML05: Mutational burden and heterogeneity in uveal melanoma (um)**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Uveal melanoma, both primary and metastatic tumours.
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)	Primary UM: mostly single (enucleation samples), up to 4 tissue cores.

It is assumed that in addition there will be one germline sample per patient.	The Liverpool Ocular Oncology Centre sees approx. 230 new UM patients per annum, with approx. 80 of these patients undergoing enucleation for treatment. These globes are sent fresh to the Pathology Dept, enabling fresh tumour (and normal choroid) collection. Collaboration with Aintree University Hospital (AUH) and other hepatic surgical centres across the Melanoma UK network. Samples in this case will mostly be resection samples as well as potentially some undergoing laparoscopy. 1- 4 cores from each patient.
# cores per tumour (if multi-region biopsying proposed)	Depending on tumour size, 2-4 punch biopsies from differing areas of the UM can be taken, to examine for intratumour heterogeneity. All samples will be associated with complete clinical and histomorphological data. Metastatic UM: likely to be mostly single samples.
Follow-up samples following first ascertainment	
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	1. Assess primary UM for intratumoral heterogeneity using high-resolution techniques 2. Compare with TCGA findings, performed retrospectively on a small cohort of 80 primary UM only. 3. Compare primary UM with metastatic UM, where possible. 4. Examine the prevalence of neoantigens, and whether these are shared or private in different tumour cores, which may determine response to therapies.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Uveal melanoma is a rare disease for which there remains no effective therapy for metastatic disease. Few systematic studies have investigated the incidence of mutations in multiple samples using comprehensive sequencing approaches. One exception is the TCGA project (to which we contributed 30 samples), which sequenced 80 primary samples. The full analysis is yet to be published from this. In the proposed project we would aim to validate the findings from the UM TCGA, as well as identify novel genes in this larger dataset. We also aim to include a proportion of metastatic tumours to compare the genetic makeup of primary and metastatic tumours. Our intention is to additionally investigate the extent of heterogeneity in UM tumours as well as its effects on neoantigen generation and antigenicity.

Is this sub-study dependent on a particular turnaround-time for sample→clinical result? State necessary TAT	No
Is this sub-study dependent on using diagnostic biopsy material?	At diagnosis: Yes Post diagnosis: Yes
Is follow-up with ctDNA important/essential in this cohort?	Not essential; however, it could be of interest in UM patients who have been identified as having a high-risk of developing liver metastases. Blood samples are taken on all UM patients undergoing the initial ocular surgical procedure; hence, these plasma samples would be available at time of diagnosis, and at follow-up ophthalmic and surveillance examinations (e.g. 6 monthly).
Is any other type of molecular analysis of the tumour proposed as part of study of this (e.g. RNA- seq, methylation analysis)?	The TCGA undertook these examinations on 80UM; it would be of value to confirm not only their genetic but also epigenetic and transcriptional findings in a prospective well-defined cohort of primary UM. Furthermore, the examination for the development of neoantigens between primary and metastatic UM would be of clinical relevance for predicting response to immunological therapies.
Numbers of WGS proposed and recruitment projection	
How many patients do you plan to recruit in total to this cohort? How many WGS would it be proposed were used on this cohort?	a. 160 (80/year) enucleations for primary UM; 5/year for metastatic UM b. 120 (60/year) enucleations for primary UM; 5/year for metastatic UM
How many patients meeting this cohort eligibility present in England per year?	250/year enucleations for primary UM; 200/year for metastatic UM
What number of patients of this cohort eligibility do you anticipate recruiting to 100KGP per year (factoring in non-consent, failure to obtain appropriate samples, technical failure of samples)?	Up to 60 for primary UM; 15 for metastatic UM.
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?	The study is not specifically aligned to a clinical trial. However, a large metastatic UM trial (SelPac) is currently recruiting in the UK (13 centres, total of 123 patients recruited over next ~2 years). This study has embedded translational research which does not currently include WGS. While this would be a desirable addition, use of samples may be limiting due to existing tissue requirements.
Is this sub-study a new therapeutic trial?	N/A

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	**Melanoma cancer**
Project title *(max 150 characters)*	**Melanoma 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.