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

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

GeCIP Lung Domain Questions to be addressed:

- Tumour genomics of Early stage pre-invasive lung cancer
- Genomic evolution and Clonal Heterogeneity of Lung cancer
- Circulating biomarkers in lung cancer and correlation with somatic genomic profiles
- Relationship of somatic genomic events with lung cancer pathologies
- Germline genomics predictors of lung cancer

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)*

Lung cancer is caused by uncontrolled cell growth in the tissue of the lung. There are two main types – small-cell lung carcinoma, and non-small cell lung carcinoma. Worldwide, it is the most common cause of cancer-related death in men, and the second most-common in women. The vast-majority (~85%) are due to long term tobacco smoking and the remaining cases are due to air pollution (e.g asbestos, second-hand smoke etc.) or rare inheritied types of lung cancer. The lung cancer GeCIP domain will study the DNA of patient's normal non-cancer tissue (germline) and tumour (somatic) to better understand:

- what changes occur in the somatic DNA as the cancer spreads (metastases) through the lung and the rest of the body, and whether these can be used to identify tumurs that are particularly liable to spread;
- whether there are certain signatures in the germline DNA that might predispose individuals to getting lung cancer;
- whether there are variations in the somatic DNA that cause a tumour to be particularly resistant or susceptible to treatment;
- how a patient's DNA effects how susceptible they are to lung cancer based on their risk factor 'load' e.g. can we better identify form the DNA of all female smokers, who will develop particularly aggressive lung cancer?

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

Lead Applicant(s)	
Name	Charles Swanton
Post	Group Leader
Department	Research Department of Oncology
Institution	University College London Hospitals NHS Trust & the Francis Crick Institute
Current commercial links	CRUK

Gear 2 Substudy leads
LG01: Stage IV disease – 1st & 2nd Line
LG02: Oligometastatic cohort
LG03: recurrence following radical radiotherapy / chemoradiotherapy
LG04: Surgically resectable disease - Lung TRACERx
LG05: Mesothelioma

GeCIP domain - Expression of interest

Full proposal	
Title*(max 150 characters)*	**Lung cancer**

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.*

Introduction

Lung cancer is associated with dismal outcome. The leading cause of cancer-related death, it accounts for nearly 1.4 million deaths worldwide every year, including more than 342,000 deaths in Europe and 162,000 in the US. 'Non-small cell' lung cancer (NSCLC) is the most common form. Despite surgery and adjuvant chemotherapy, the overall 5-year survival remains 67% for stage IB, 49% for stage II and 39% for stage III NSCLCs. Less than 5% of patients presenting with Stage IV metastatic disease are alive at 5 years.

Outline of Plans for Lung Cancer Research and Discovery

Our proposed GeCIP domain brings together NHS clinicians (respiratory, oncology, pathology), bioinformaticians, immune-biologists, basic and functional biologists and somatic and germline genomics experts nationally within one group to foster a more complete understanding of the following key questions pertinent to lung cancer. Importantly, trainees in each of these areas will be invited onto the GeCIP panel to build future infrastructure in the UK and within the NHS, and training will be a high priority area. Our domain will focus on questions relevant to patient outcome, NHS service provision, lung cancer disease biology and patient stratification for therapy. In particular the domain strategy will be focussed on:

1. Tumour Evolution and Adaptation Subdomain: Swanton, Le Quesne, Middleton, Janes, Campbell, Fennell, Van Loo, Luscombe
    a. Identifying how lung cancers (NSCLC/SCLC/Mesothelioma) adapt and evolve through treatment and over time: ideally focus on tumour material where primary and matched paired metastatic biopsies and germline DNA are available with in depth clinical annotation.
    b. Identifying the origins of the lethal subclone and how does therapy affect the subclonal composition of the relapsed tumour
    c. Identification of drivers of cancer progression, diversification and adaptation/drug resistance; identification of combinatorial driver events that canalise tumours through distinct histological trajectories.
    d. Develop a deeper insight into pre-invasive lung cancer and the early somatic events that govern or constrain future tumour development- identify new therapeutic targets to limit cancer evolution
    e. Examine how mutational processes in lung cancer genomes evolve over time and influence mutational burden and functional cell behaviour (drug resistance, migration, invasion, immune detection and evasion etc)
    f. Develop national longitudinal studies in Mesothelioma and Small Cell Lung Cancer similar to TRACERx for inclusion into the Lung program.
    g. Improve our understanding of lung adenocarcinoma cellular phenotypes to provide a subclassification system related to genomic changes.
2. Rare Lung Cancer Cohort Subdomain: Houlston, Swanton, Campbell, Fennell
    a. Address the preponderance of distinct molecular cohorts of lung cancers within individual patient groups e.g. why are female non-smokers particularly susceptible to the acquisition of EGFR activating mutations or ALK rearrangements?

b. Address the transformation of particular NSCLC entities- eg NSCLC to Small cell transformation and the genomic drivers of adenosquamous carcinoma
c. Decipher therapeutically tractable events in malignant mesothelioma

3. Immunobiology Subdomain Quezada/Peggs/Swanton/Middleton
   a. Address how the immune microenvironment edits and constrains tumour evolution?
   b. Identify and validate new genomic markers predictive of benefit from immunotherapy

4. Radiation Oncology Subdomain: Faivre Finn/ Hiley
   a. Address influence of radiation therapy on emergent resistant disease genomic landscape
   b. Identify somatic and structural variants associated with disease relapse following radical radiation which could serve as potential biomarkers for dose escalation.
   c. Identify genomic signatures associated with deficiencies in pathways of DNA damage repair and correlation with clinical outcome (e.g HR & NHEJ).
   d. Discovery of novel germline variants associated with excess radiation induced normal tissue toxicity
   e. Define margins of early stage NSCLC with microscopic residual disease to improve radiation targeting

5. Circulating Biomarker Subdomain: Dive/Shaw/Swanton/Cookson/Moffat
   a. Through warm autopsy programs the GeCIP will address how well circulating free tumour DNA and the CTC fraction reflects tumour diversity in the primary and metastatic tumour.
   b. Generate new approaches to single cell genomics and early diagnosis

6. Germline Subdomain: Houlston/Bowcock/Turnbull
   a. Discovery of novel genomic variants conferring risk of lung cancer (case- control analysis against remainder of 100KGP cohort), identifying new germline variants predisposing to risk of lung cancer and chronic lung disease
   b. Characterisation of lung cancer cohort by germline findings and analysis of somatic mutational profile in relation to germline mutational status
   c. Analysis of germline data for mutations in genes included in (looked for) secondary findings gene list (MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MutYH, BRCA1 and BRCA2, VHL, MEN1, RET, RB1)
   d. Lung cancer risk prediction modelling utilising germline findings. Selection of high risk individuals for lung cancer CT screening programmes.

The work in this area will be undertaken in collaboration with the interpretation, validation and feedback domain likely in close concert with parallel activities within the inherited Cancers Domain

7. NHS Infrastructure Subdomain: Medical/ClinicalOncologists/Respiratory Physicians/Pathologists and Health Informatics and Bioinformatics.
   a. Adapt GMC research and clinical infrastructure to the changing nature of research brought about by 100K Genome project. Integrate projects within biobanking procedures for all new cancer patients treated within the NHS.
   b. Adapt clinical electronic medical records to integrate with genomics medicine (FARR institute).
   c. Standardise clinical data collection from patients treated with standard of care and clinical trial cohorts for integration within the Lung GECIP

d. Expedite the use of WGS to better to define patients with disease sensitive and resistant to standard of care platinum therapies
e. Expedite the use of WGS to support NHS infrastructure and inform treatment approaches in real-time
f. Develop standards for actionable variant calling for patient stratification into clinical trials or standard of care therapies

8. Clinical, Informatics and Research training Subdomain Jamal-Hanjani, Mulatero, Hiley.

9. Functional Genomics Subdomain: Downward, Sahai, Svejstrup.
   a. Decipher role of new genomic drivers of lung cancer biology and signal transduction pathways through which they operate
   b. Understand role of the tumour microenvironment in constraining lung cancer evolution
   c. Exploit lung cancer genomics datasets to understand how lung cancer genomic instability arises

Current Funding and Plans for Procurement of Funding for Research Activities

The consortium has been selected to encompass funding from all major research bodies in the United Kingdom. Swanton is a senior group leader, to be based at the Francis Crick Institute in 2015 (MRC/Wellcome Trust and Cancer Research UK). Swanton's funding is derived from Cancer Research UK, Medical Research Council, UCLH Biomedical Research Centre, Prostate Cancer Foundation, Breast Cancer Research Foundation and the European Research Council. He receives programmatic support for TRACERx together with funding from Boehringer and Roche Genentech to support clinical trial activity around TRACERx. Some of the research activities proposed by the GeCIP domain will take place within the TRACERx study, which has been awarded funding from Cancer Research UK (£10.5 million), the NIHR UCLH BRC (£500,000), the Rosetrees Trust (£345,000) and the Academy of Medical Sciences (£30,000). Janes is funded by the Wellcome Trust and Roy Castle Foundation to study pre-invasive lung cancer. Campbell is funded by Wellcome Trust to study the genomics and evolution of lung cancers. Dive receives core institute funding from CRUK for circulating biomarker work and Middleton is the Chief Investigator for the CRUK funded Matrix clinical trial (21 arm clinical trial in collaboration with Astra Zeneca and Pfizer). Between the group we have substantial grant funding to support this endeavour and mechanisms in place to write grants to fund additional work within each subdomain. Field has core funding from the Roy Castle Lung Cancer Foundation, as well as NIH and EU funding for genomics and biomarker projects. Shaw has substantive funding from CRUK for circulating biomarker work in breast, pancreas and melanoma

Opportunities for Education and Training Lead: Dr Jamal-Hanjani

The GeCIP domain consists of trainees in subject areas including clinical medicine, pathology, basic cancer research and bioinformatics. With advances in next-generation sequencing and the need for precision medicine to improve clinical outcomes, reduce toxicity and increase cost effectiveness, there is a need to move toward the implementation of genomics in everyday clinical practice. Clinicians will need to adapt to the challenges this will pose in terms of data analysis and interpretation, as well as the ethics of communicating such data to patients. Working with Genomics England will offer trainees the opportunity to develop the skillset required to analyse and interpret sequencing data alongside detailed clinical annotation, radiological and clinical examination. Clinical trainees stand to benefit significantly by working with scientists and bioinformaticians in the field of cancer genomics. A better understanding of the methods involved in analysing and validating sequencing data will improve their appreciation of the complexities, yet potentially powerful application of such data in clinical practice.

In the studies included this application, clinical and bioinformatics trainees will be given the opportunity to partake in research projects analysing sequencing data from patient tumours in the context of detailed clinical annotation. The intention here will be to map the genomic profile of each patient, with an emphasis on disease pathogenesis and the identification of potential predictive and prognostic genetic markers of disease and treatment response. With detailed clinical and sequencing datasets for each patient, novel and/or targeted therapies will also be assessed in the relapsed or metastatic setting using a specifically designed MiSeq panel (NEQAS accreditation expected in early 2015) of common known driver mutations and actionable mutations in lung cancer. This panel is used in a clinical diagnostic facility and manufactured to GCLP standards. Overall this domain aims to link, and encourage collaboration between, all domains covering generic aspects of GeCIPs such as training, transformation and implementation. Although there will be specific considerations for each domain, the overall objectives and outcomes can be achieved with standardised initiatives and pathways.

Patient Stratification
In partnership with industry we will endeavour to use the 100KGP data in the lung domain to initiate treatment matching algorithms, genomic risk stratification platforms and protocols with the goal of improving treatment outcomes for patients with lung cancer or at risk of lung cancer. Risk prediction modelling for selecting high risk individuals for lung cancer CT screening trials (John Field)

Defining Standards for Variant Annotation
Improving algorithms for defining robust actionable variants from longitudinal and spatially separated samples is an area of unmet clinical need. The Lung GECIP will work closely with industry to define industry-standards for variant calling.

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.*

Proposed UK Leader
Charles Swanton is the proposed leader of the lung GeCIP and holds an honorary consultant NHS contract with University College London Hospitals NHS Trust. Charles is a tenured senior group leader of the Cancer Research UK London Research Institute Translational Cancer Therapeutics laboratory, the Co-director of the CRUK UCL Lung cancer centre of excellence, and Chair in Personalised Cancer medicine at University College Hospital and Cancer Institute. He is chief investigator of the TRACERx Lung cancer longitudinal clinical study (TRAcking Cancer Evolution through therapy). This 850 patient study aims to decipher how lung cancers change and adapt to therapy over the disease course and how a knowledge of cancer heterogeneity can be used to improve treatment outcomes for patients.

GeCIP Skills and Representation of Expertise
The lung GeCIP has broad expertise in the following areas:
Medical and Clinical Oncology: Charles Swanton, Siow-Ming Lee, Sanjay Popat, Yvonne Summers, Fiona Blackhall, Dean Fennell, James Spicer, Christian Ottensmeier, Gary Middleton, Peter Schmid, Mariam Jamal-Hanjani, Crispin Hiley, Corrine Faivre-Finn.
Clinical trial recruitment and leadership: Siow-Ming Lee, Sanjay Popat, Yvonne Summers, Fiona Blackhall, Dean Fennell, James Spicer, Christian Ottensmeier, Gary Middleton, Peter Schmid, Tobi Arkenau, Clive Mulatero
Lung Cancer CT Screening trial recruitment and Risk Prediction Modelling: John Field
Respiratory Physicians and Pre-invasive disease experts: Sam Janes, Richard Booton

Clinical Genetics Physicians: Richard Houlston, Clare Turnbull
Respiratory Genomics: Anne Bowcock, Miriam Moffatt, William Cookson
Pathology: John LeQuesne, Elaine Borg, Keith Kerr, Andrew Nicolson, Jane Moorhead, Diaz Cano, Barnaby Clark
Functional Biology: Erik Sahai, Julian Downward FRS, Jesper Svejstrup FRS
Lung Cancer Genomics: David Gonzalez De Castro, Charles Swanton, Elza De Bruin
Germline Genomics : Richard Houlston, Clare Turnbull, Anne Bowcock,
Cancer Bioinformatics: Nicholas Luscombe, Nicholas McGranahan, Gareth Wilson, Nicolai Birkbak, Paul Bates, Christopher Steele, Julie Bertrand, Richard Mitter
Health Informatics FARR Institute: Harry Hemingway
Lung Cancer Evolution and Mutational Signatures: Elza De Bruin, Nicholas McGranahan and Charles Swanton.
Cancer Circulating Biomarkers: Caroline Dive and Jacqui Shaw, John Field
Training: Mariam Jamal-Hanjani (Medical Oncology) and Crispin Hiley (Clinical Oncology), David Moore (Pathology), Adam Januszewski (Oncology) and Nicholas McGranahan (Bioinformatics)
Immunology: Sergio Quezada, Karl Peggs

Patient Advocacy:
The lung GeCIP domain will work with the Independent Cancer Patients' Voice (ICPV) patient advocate group, which has been involved in the set-up of clinical studies such as TRACERx. We have valued their input and implemented their suggestions regarding study protocol and patient documents in the past, and we will rely on their input regarding our work within the domain as part of Public and Patient Involvement.

Potential International Collaborators
Trever Bivona MD PhD (UCSF), Govindan Ramaswamy MD PhD (Washington University), Carlo Maley PhD (UCSF) and Zoltan Szallasi MD PhD(Harvard/Danish Technical University).

Mechanisms for Pre-competitive Interaction with Industry
Our GECIP domain has extensive experience in interactions in drug development and collaborations with the pharmaceutical industry. Many of our contacts (Roche, Novartis, Boehringer Ingelheim) have expressed interest in ongoing interactions with the lung GECIP. In particular our discussions have focused on the following key areas of industry interaction:

Novel Targetable Gene Fusions and Therapeutic Opportunities
The Lung GECIP will be particularly vigilant for recurrent gene fusions deciphered by whole genome sequencing approaches through the GEL 100KGP that may be targetable and lead to novel stratification approaches and therapeutic targeting in collaboration with industry. Our links with the National Matrix trial (Middleton PI) will enable us to quickly react to these genomic events and design clinical substudies within Matrix to treat patients.

Circulating Biomarker Collaborations
In parallel, our GECIP has extensive collaborations with industry in the field of Circulating Biomarkers (both CTC and cfDNA Caroline Dive and Jacqui Shaw) with several distinct circulating tumour cell platforms in situ in the Manchester Research Institute to attempt to profile genetic aberrations identified from the 100KGP in peripheral blood from patients. This will allow rapid translation from bench to bedside of scientific discoveries made within the GECIP for patient stratification.

Gear 2 substudy proposals

Gear 2 Eligibility Criteria **Pre- and post-operative cfDNA collection** - Stage I-IV **Multiregion (multiple samples/cores taken ex-vivo from a single resected tumour mass)** - Surgically resected NSCLC: up to 4 regions **Multitumour (disparate sites of tumour deposition collected synchronously)** - Multiple primary lesions: 2 or more spatially distinct primary lung tumours Advanced disease: (a) NSCLC up to 4 samples of primary tumour, lymph nodes and/or distant metastases including NSCLC stage IV with oligometastatic disease; (b) NSCLC IIIB-IV with local regional relapse following radical radiation or chemoradiation **Longitudinal** - Paired samples pre-and post- administration of neoadjuvant chemotherapy; Paired samples pre-and post- administration of 1st line treatment in metastatic setting; Sampling of tumour recurrence or metastasis is invited for any patient with a previous successfully sequenced tumour
LG01: Stage IV disease – 1st & 2nd Line Assessment of germline risk associated with disease in non-smokers (EORTC 08114). Assess mechanisms of resistance to platinum doublet chemotherapy. Although the mechanism of resistance to EGFR TKI's have been studied in a large proportion of cases the underlying cause remains unclear. This study would allow greater resolution on the study of treatment resistance in patients lacking more common resistance mechanism T790M.
LG02: Oligometastatic cohort Presentation of patients with oligometastic disease is increasingly common given availability of axial imaging. Determination of true oliogmetastatic state prior to local ablative therapy would help determine appropriateness of local therapy. This study would contribute to our understanding of radiation resistant mechanisms.
LG03: recurrence following radical radiotherapy/chemoradiotherapy It is likely that mechanisms of resistance will involve complex chromosomal rearrangements only discoverable by WGS. Defects in DNA damage response signalling are also likely to be important and mutational signatures to look at homologous recombination defects (genomic scars etc) would require WGA
LG04: Surgically resectable disease - Lung TRACERx Assessment of intratumour heterogeneity of genomic variants outside of whole exome that impact on tumour evolution, genomic instability and clinical outcome.
LG05: Mesothelioma Assessment of germline risk associated with mesothelioma (BAP1 has been proposed). Assess mechanisms of resistance to platinum doublet chemotherapy. Define mechanisms underpinning exceptional response to novel agents in clinical trial

Detailed research plan – Cancer Main Programme Gear 2 studies

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**LG01: Stage IV disease – 1st & 2nd Line**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	NSCLC – IIIB/IV. Pre or post 1st line treatment in metastatic setting. EGFR mutant or EGFR Wildtype
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 at baseline prior to treatment in the metastatic setting.
# cores per tumour (if multi-region biopsying proposed)	NA
Follow-up samples following first ascertainment	Paired sample following progression on 1st or second line treatment would be requested if clinically appropriate.
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	Assess mechanism of resistance to common therapies such as platinum doublet chemotherapy and EGFR TKI
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Assessment of germline risk associated with disease in non-smokers (EORTC 08114). Assess mechanisms of resistance to platinum doublet chemotherapy. Although the mechanism of resistance to EGFR TKI's have been studied in a large proportion of cases the underlying cause remains unclear. This study would allow greater resolution on the study of treatment resistance in patients lacking more common resistance mechanism T790M.
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 are a number of proposed clinical trials that this cohort could be aligned to that would allow collection of longitudinal data. Patients from this cohort would feed into established clinical trials such as the Lung Matrix Study.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**LG02: Oligometastatic cohort**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	NSCLC. Stage IV with oligometastatic disease.
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)	Samples from different oligometastatic sites would sites would be eligible (max 3 per

It is assumed that in addition there will be one germline sample per patient.	patient).
# cores per tumour (if multi-region biopsying proposed)	NA
Follow-up samples following first ascertainment	Subsequent single samples at the time of oligometastatic or disseminated progression would be accepted.
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	The analysis of multiple sites of disease at presentation would allow origin of oligometastatic disease to be determined (monoclonal vs polyclonal). Samples of subsequent progression following ablative therapy (SBRT or RFA) could be correlated with primary disease to assess divergence and genetic aberrations generating radiation resistance.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Presentation of patients with oligometastic disease is increasingly common given availability of axial imaging. Determination of true oliogmetastatic state prior to local ablative therapy would help determine appropriateness of local therapy. This study would contribute to our understanding of radiation resistant mechanisms.
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 cohort would require patients to be co-recruited to one of the oliogometastatic disease trials with a NSCLC cohort in the UK (SARON, CORE, HALT)
Is this sub-study a new therapeutic trial?	

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**LG03: recurrence following radical radiotherapy/chemoradiotherapy.**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	NSCLC. Local regional relapse following radical radiation or chemoradiation. IIIB-IV
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.*	At the time of local or metastatic recurrence following radical radiotherapy biopsy may be indicated on clinical grounds. An additional tissue sample will be obtained for WGA.
# cores per tumour (if multi-region biopsying proposed)	NA
Follow-up samples following first ascertainment	Samples from local sites of relapse (within field)

	are requested. Samples from synchronous metastatic recurrences would be accepted if accompanied with region from area of local recurrence. Metachronous sites of metastatic relapse would be accepted for patients recruited to this cohort.
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	Mechanisms of resistance to radiation therapy are poorly understood. Genomic aberrations caused by ionising radiation are likely to be structural variants rather than single nucleotide variants. Whole analysis would be required to investigate mechanism of resistance. Clinical data on patient characteristics, radiotherapy treatment and disease free intervals will be obtained.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	It is likely that mechanisms of resistance will involve complex chromosomal rearrangements only discoverable by WGS. Defects in DNA damage response signalling are also likely to be important and mutational signatures to look at homologous recombination defects (genomic scars etc) would require WGA
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?	Ideally we would like to recruit this cohort in the context of a longitudinal study. The following study is in development at three UK sites and can be expanded. SIEVERT: Sampling Intra-thoracic tumour EVolution following External beam Radiation Therapy (SIEVERT) Study: A prospective tissue collection study Rebiopsy of patients will only occur for a clinical indication (diagnostic biopsy required to obtain further tissue etc). Collection of tissue samples will use existing research resources.
Is this sub-study a new therapeutic trial?	No. But may identify patients with DDR defect suitable for an AZ trial in development (basket trial of DDR inhibitors).

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**LG04: Surgically resectable disease - Lung TRACERx**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	NSCLC – early stage surgically resectable disease. No neo-adjuvant chemotherapy. See attached clinical trial summary. Excluded – T1 N0 disease.
Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)	Multi-region samples taken as per standard Lung TRACERx protocol from surgically resected

It is assumed that in addition there will be one germline sample per patient.	specimens. One of these tumour regions to be processed by local GMC for WGA.
# cores per tumour (if multi-region biopsying proposed)	If the use of biopsies/bronchoscopy samples to recruit people with advanced disease is not feasible then TRACERx will be relied upon more heavily as a way to recruit patients with surgically resectable disease and provide good quality longitudinal follow-up data. In that scenario we propose the use of multi-region whole genome sequencing.
Follow-up samples following first ascertainment	NA
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	WGA of a single tumour region would allow discovery of novel translocations, regulatory variants associated with disease and improved characterisation of mutational signatures etc. These could then be looked for, by TRACERx trial team, in multi-region TRACERx samples (outside of GE) to look at heterogeneity of genetic aberrations that would be outside of the standard whole exome sequencing within the TRACERx trial. Multi-region whole genome sequencing would allow assessment of intra tumour heterogeneity of regulatory variants, allow fine resolution of mutational signatures and detect of novel translocations.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Assessment of intratumour heterogeneity of genomic variants outside of whole exome that impact on tumour evolution, genomic instability and clinical outcome.
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 cohort is aligned to the lung TRACERx cohort which will eventually feed into the DARWIN trial cohorts in the 1st line metastatic setting if patients relapse and potentially the lung matrix study in the second line. Recruitment to this cohort would require mandatory recruitment to TRACERx.
Is this sub-study a new therapeutic trial?	No but patients may feed into the DARWIN I and II trials if they relapse with stage IIIB/IV disease. Projects at an advanced stage of development (Boehringer Ingelheim & Roche).

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**LG05: Mesothelioma**

Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Mesothelioma - epithelioid, sarcomatoid, biphasic - Surgically resectable or eligible for VATs biopsy, chemonaive - Clinical trial cohort (eg. CRUK phase 1 FAK, PD1 inhibitor)
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 at baseline prior to treatment.
# cores per tumour (if multi-region biopsying proposed)	
Follow-up samples following first ascertainment	Paired sample following progression on 1st or second line treatment would be requested if clinically appropriate.
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	- To robustly define a signature for asbestos induced mesothelioma - Define the genomic architecture of mesothelioma to identify novel potentially actionable targets - Assess mechanism of resistance to common therapies such as platinum doublet chemotherapy - To define the mechanism of exceptional response and resistance to novel clinical trial drugs to facilitate treatment stratification
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Assessment of germline risk associated with mesothelioma (BAP1 has been proposed). Assess mechanisms of resistance to platinum doublet chemotherapy. Define mechanisms underpinning exceptional response to novel agents in clinical trial
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 are a number of proposed clinical trials that this cohort could be aligned to that would allow collection of longitudinal data. Eg. phase 1 FAK/PD1 trial in which fresh frozen tissue samples will be acquired Other clinical trials may be aligned
Is this sub-study a new therapeutic trial?	Yes – cancer research UK would be the proposed partner. Trial in development aiming to enrol in 2016

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	Lung cancer
Project title *(max 150 characters)*	Gear 2 substudies

Applicable Acceptable Uses. *Tick all those relevant to the request and ensure that the justification for selecting each acceptable use is supported in the 'Importance' section (page 3).*

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.