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

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

Our proposed GeCIP domain brings together NHS clinicians (surgeons, oncologists and pathologists), somatic and germline genomics experts, bioinformaticians, immuno-biologists, basic and functional biologists. An RCC tissue collection protocol has been in place for the last two years, operating successfully across three NHS trusts, with two additional sites joining this year. There is a considerable infrastructure in place with dedicated tissue collectors, research nurses and clinical fellows who coordinate tissue, blood and urine collection, storage and processing as well as clinical follow-up and data collection. In addition to cases of ccRCC the GeCIP will contribute less common RCC subtypes including chromophobe and papillary cancers. Another major focus will be on those cases with multiple or multifocal tumours, early age of onset or family history of RCC. Finally, matched primary-metastatic pairs will be included. Germline DNA will be isolated from peripheral blood in all cases. Robust clinical annotation and longitudinal follow-up will be available for all cases. The domain will focus on questions relevant to RCC biology, patient outcomes, and patient stratification for therapy.

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)*

There are about 10,000 cases of renal cell carcinoma (RCC), cancer of the kidney, in the UK each year, of which about 75% are of clear cell subtype (ccRCC). The other subtypes, papillary and chromophobe, account for most of the remaining cases. Although a number of diseases have been identified that cause predisposition to kidney cancer, the majority of cases are sporadic i.e. they are seemingly random. Despite increased detection of early disease, for a quarter of patients their cancer has spread from the kidney to other parts of their body, called metastatic disease, when they are first diagnosed. Similarly, around a quarter of patients progress to metastatic disease following surgery to remove the lump. Metastatic disease is incurable with half of patients dying within two years of diagnosis and approximately 4000 deaths per year in the UK.
Despite advances in our understanding of kidney cancer, this has not translated into new medicines. Thus, many patients receive futile treatment at considerable cost, both economic and in terms of side effects. Arguably therefore the greatest challenge in this disease is to translate the ongoing increased understanding of biology into benefit for patients in the clinic. The Renal Cancer GeCIP domain will carry out research on the 100,000 Genomes Project dataset with this as their primary goal.

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

Lead Applicant(s)	
Name	James Larkin
Post	Consultant Medical Oncologist FRCP PhD
Department	

Institution	Royal Marsden Hospital
Current commercial links	

Gear 2 Substudies
Small renal masses/Leibovich 3 or less n=50 patients
Primary and LN involvement or metastatic disease or both for M-Seq of all involved n=50 patients
Multifocal/bilateral and/or end-stage renal disease n=20 patients
Non-clear cell including mixed morphologies after microdissection n=20 patients
Analysis of hypoxia pathway transcription factor binding sites (e.g. by ChIP-seq) and mutations at those sites n=20 patients
Germline analysis, e.g. for new genes and mutations of the known RCC genes, especially cases with no "syndromic" features n=20 patients
Pre- and post-treatment with systemic therapy outside trials n=20 patients
Co-recruitment into TraceRx RCC, ADAPTeR and A-PREDICT n=50 patients

GeCIP domain - Expression of interest

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

Our proposed GeCIP domain brings together NHS clinicians (surgeons, oncologists and pathologists), somatic and germline genomics experts, bioinformaticians, immuno-biologists, basic and functional biologists. An RCC tissue collection protocol has been in place for the last two years, operating successfully across three NHS trusts, with two additional sites joining this year. There is a considerable infrastructure in place with dedicated tissue collectors, research nurses and clinical fellows who coordinate tissue, blood and urine collection, storage and processing as well as clinical follow-up and data collection. In addition to cases of ccRCC the GeCIP will contribute less common RCC subtypes including chromophobe and papillary cancers. Another major focus will be on those cases with multiple or multifocal tumours, early age of onset or family history of RCC. Finally, matched primary-metastatic pairs will be included. Germline DNA will be isolated from peripheral blood in all cases. Robust clinical annotation and longitudinal follow-up will be available for all cases. The domain will focus on questions relevant to RCC biology, patient outcomes, and patient stratification for therapy.

a) RCC genomics at different disease stages and relationship to clinical outcome

We will profile nephrectomy specimens obtained at surgery. Importantly in RCC, patients still undergo resection of the primary tumour in the presence of metastatic disease, providing us with a cohort of tumours representative of all disease stages (I-IV). We will establish whether the overall number of driver somatic mutations and whether mutations in particular genes correlate with disease stage and outcome. Further, when these patients receive systemic therapy we will correlate therapeutic response with specific genomic profiles. We will also asses how intratumour heterogeneity affects the disease course both in terms of disease progression and therapy response.

b) Contribution of clonal evolution to metastases and drug resistance in RCC

Significant genetic diversity between primary and metastatic lesions has been identified in solid tumours, including RCC. By profiling matched samples (primary-metastases, and responding-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 biomarker opportunities.

c) Cell-free tumour DNA in RCC and its correlation with tumour genomic profiles

Tumour cell-free DNA will be isolated from plasma and urine of tissue donors. The GeCIP will address how tumour-free DNA reflects the genomic composition of the primary and metastatic tumours. We will also explore whether mutations detected in tumour-free DNA can predict disease relapse and inform the mechanisms of treatment resistance.

d) Germline genomics in RCC

By profiling germline DNA the GeCIP will identify novel germline mutations that predispose to RCC. We will focus especially on patients who present multiple tumours, multi-focal tumours, have a family history of RCC and early age of onset, but in whom known germline predisposition genes are not mutated. We will also correlate the presence of germline variants with the somatic genomic landscape and clinical behaviour. The work in this area will be undertaken in collaboration with the inherited Cancers Domain.

e) Immunology

As increasing numbers of RCC patients are treated with immunomodulating agents, the GeCIP will have the opportunity to identify and validate genomic alterations which predict response to immunotherapy.

f) Functional validation

Gene candidates which are potential novel disease drivers and biomarkers will be functionally validated using in vitro and in vivo approaches, to identify new potential therapeutic targets and further illuminate disease biology.

Proposed additional research activity

The whole genome sequencing data will be complemented by gene expression and proteomic data for a subset of patients. All the patients recruited into these studies will be followed-up long term with ongoing data collection regarding clinical outcomes. Wherever possible further tissue will be sought and profiled in the event of disease progression.

Current funding and plans for procurement of funding for proposed research activities

The GeCIP encompasses funding from all major research bodies in the United Kingdom. For example, Houlston's current funding includes CRUK, EU, NIH, myeloma UK and Leukaemia Lymphoma Fund. Swanton's funding is derived from CRUK, MRC, ERC, UCLH Biomedical Research Centre, Prostate Cancer Foundation, Rosetrees Trust and Breast Cancer Research Foundation. Tomlinson is funded by CRUK and the Oxford BRC and Larkin by CRUK, the EU and the RMH/ICR BRC. Some of the research activities proposed by the GeCIP domain will take place within the "Mapping clonal evolution in renal cell carcinoma" study which is funded by CRUK through a Clinician Scientist Fellowship awarded to Turajlic. The GeCIP as a whole will have substantial grant funding to support this endeavour and mechanisms in place to write grants to fund additional work.

Opportunities for education and training

The GeCIP domain consists of trainees in subject areas including clinical medicine, surgery, basic cancer research and bioinformatics. For the clinical trainees the participation in the GeCIP will offer an opportunity to learn about the challenges associated with next generation sequencing data and its interpretation. Further, as we move towards implementation of genomics in everyday clinical practice the trainees will learn how these data can be used to improve clinical outcomes and how to communicate it to their colleagues and patients. For the bioinformatics trainees there will be an opportunity to analyse large data sets in the context of clinical annotation and potentially identify prognostic and predictive biomarkers. For the basic cancer research trainees there will be an unprecedented opportunity to inform their bench-work by large genomic datasets. The joint training leads for our domain, Turajlic and Swanton, will ensure that the needs of trainees are looked after and new trainees are welcomed and inducted into the domain.

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.*

NHS Clinicians

Uro-Oncology: James Larkin (RMH), Sarah Rudman (GSST), Tim Eisen (Addenbrooke's), Naveen Vasudev (Leeds Institute of Cancer and Pathology), Fiona Thistlethwaite (Christie), Hilary Glen (University of Glasgow).

Renal Surgery: Tim O'Brien (GSST), Michael Aitchison (RFH), Grant Stewart (University of Edinburgh), Grenville Oades (University of Glasgow)

Renal Pathology: Steve Hazell (RMH), Ashish Chandra (GSST), Stewart Fleming (Dundee)

Academics
Sporadic Renal Cancer Genomics: Charles Swanton (LRI)
Inherited Renal Cancer Genomics/Clinical Genetics: Richard Houlston (ICR), Ian Tomlinson (University of Oxford), Eamonn Maher (University of Cambridge), Clare Turnbull (RMH/ICR)
Nephrology/Clinical Genetics: Robert Kleta (UCL), Daniel Gale (UCL)
Renal Cancer Biology: Peter Ratcliffe (University of Oxford), David Mole (University of Oxford), Athena Matakidou (Cambridge Research Institute)
Renal Cancer Biomarkers: Rosamonde Banks (Leeds Institute of Cancer Biology)
Cancer Bioinformatics: Stuart Horswell (LRI), Rafik Salama (University of Oxford)
Immunology: Sergio Quezada (UCL), Karl Peggs (UCL)
Trainees: Samra Turajlic (LRI/RMH medical oncology/sporadic genomics), Mark Stares (RMH/medical oncology), Aspasia Solutati (GSST/Medical Oncology), James Whitworth (University of Birmingham/biology), Maxine Tran (Addenbrooke's/surgery/biology), Seb Trainor (Leeds Institute of Cancer and Pathology)

Proposed UK leader for the domain
The proposed UK Leader is Dr James Larkin, Consultant Medical Oncologist at the Royal Marsden Hospital who specialises in the treatment of RCC. Since 2012, he has been the Chair of the NCRI RCC Clinical Studies Group and of the Royal Marsden/Institute of Cancer Research Committee for Clinical Research. More recently he acted as the Chair of the Organising Committee for the European International Kidney Cancer Symposium (Dublin, 2014) and the GU track at ESMO (Madrid, 2014). In the last 4 years he has secured almost £10 million of grant funding as principal or co-applicant, mostly in the field of renal cell carcinoma research and in collaboration with members of the RCC GeCIP domain.

Potential international collaborators

Prof Mark Lathrope (RCC Genetics and Bioinformatics)

Mechanisms for pre-competitive interaction with partners from industry
Our GeCIP domain has extensive experience in interactions in drug development and collaborations with the pharmaceutical industry. For example Larkin and Swanton in collaboration with other GeCIP members have set up a number of academically-led clinical trials in RCC in partnership with industry in the last 5 years (E-PREDICT, Novartis, A-PREDICT, Pfizer, ADAPTeR, BMS).

Detailed research plan – Cancer Main Programme Gear 2 studies

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**RN01: Renal**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	1. Small renal masses/Leibovich 3 or less n=50 patients 2. Primary and LN involvement or metastatic disease or both for M-Seq of all involved n=50 patients 3. Multifocal/bilateral and/or end-stage renal disease n=20 patients 4. Non-clear cell including mixed morphologies after microdissection n=20 patients 5. Analysis of hypoxia pathway transcription factor binding sites (e.g. by ChIP-seq) and mutations at those sites n=20 patients 6. Germline analysis, e.g. for new genes and mutations of the known RCC genes, especially cases with no "syndromic" features n=20 patients 7. Pre- and post-treatment with systemic therapy outside trials n=20 patients 8. Co-recruitment into TraceRx RCC, ADAPTeR and A-PREDICT n=50 patients 1
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 if possible
# cores per tumour (if multi-region biopsying proposed)	4
Follow-up samples following first ascertainment	subsequent metastatic sites if possible
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	See immediately below
Scientific case and insights that will be gained from this cohort (more details, as indicated)	All proposed cohorts can be summarised as aiming to better understand disease biology for the benefit of patients, for example 1) Characterising molecular high risk features in disease conventionally scored as low risk and the converse, 2) developing rational systemic therapies above and beyond the anti-VEGF, mTOR and PD1 agents shown to of benefit in clear cell RCC and 3) generating novel germline genetic tests useful in screening potentially susceptible individuals. Further detail can be provided as necessary.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study?	• A-PREDICT: CRUK-approved multicentre phase 2 study CI James Larkin sponsor

Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	RM/ICR supported by educational grant from Pfizer • TraceRx RCC: CRUK-funded multicentre tissue collection CI Samra Turajlic • ADAPTeR: RM/ICR BRC-supported single centre phase 2 study CI James Larkin supported by educational grant from Novartis Co-recruitment is mandatory for this cohort
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	Renal 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 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.