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

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

This proposed Prostate Cancer GeCIP will focus on several key areas:

1. Molecular stratification of localised disease deemed to be low risk to identify the poor prognostic subgroup of prostate cancer patients in this category.
2. Elucidation of the molecular features of locally advanced high-risk patients in order to allow the molecular categorization of these cancers in order to distinguish good prognosis disease from those with poor prognosis disease to deliver the most appropriate treatment to each patient, minimizing risk of recurrence, delivering more precise treatment to each patient as well as decreasing overtreatment in lower risk disease.
3. Further study of the multi-focality of prostate cancer as well as the intra-patient heterogeneity of this disease, particularly comparing same patient localised and the lethal metastatic disease.
4. Molecular stratification of lethal prostate cancer in order to deliver more precise cancer care to each patient, more efficient anti-cancer drug development, and improve outcome from this disease.
5. Establish a better understanding of primary and acquired resistance mechanisms associated with currently available anticancer treatments for this disease, including hormonal deprivation and tubulin drug treatment with the taxanes.
6. Analysis of germline DNA in prostate cancer patients, particularly patients with high risk and lethal disease, with or without a family history of prostate cancer, to elucidate genomic variants that increase risk of prostate carcinogenesis.

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)*

Prostate cancer is caused by uncontrolled cell growth in the prostate, a gland in the male reproductive system that sits just under the bladder. This is primarily a problem of old age with 99% of cases occurring in males over the age of 50, and although PSA (a substance found at low levels in the blood of men with a healthy prostate, but at elevated levels in those with prostate cancer) monitoring has improved detection, it has had little effect on survival rates.

The Prostate Cancer GeCIP domain will study the DNA of patients recruited to 100,000 Genomes Project to establish what changes occur in the DNA of normal prostate that cause them to become cancerous. We hope to link these causative mutations to how severe the tumour becomes, and whether or not it reacts to treatment. In the future the hope is that by understanding the profile of each individual patient's prostate tumour i.e. what mutations have occurred and where in the DNA they have occurred, a patient's treatment can be tailored to better suit their particular type of cancer. We also hope to use this opportunity to develop drugs, or repurpose existing ones, that are specific to certain genetic types of prostate cancer.

Expected start date	**Q2 2017**

Expected end date	**Q2 2020**

Lead Applicant(s)	
Name	Professor Johann de Bono MB ChB FRCP MSc PhD FMedSCi
Post	Regius Professor of Cancer Research, Professor of Experimental Cancer Medicine, honorary consultant in medical oncology
Department	
Institution	Institute of Cancer Research/Royal Marsden
Current commercial links	

Gear 2 Substudies
PR01: Genetic analysis of markers of Prostate cancer severity in Afro-Caribbean men
PR02: Interrogating genomic scars in whole genome sequencing data of tumours from the 100,000 genomes project.
PR03: Deciphering mechanisms of early onset aggressive prostate cancer
PR04: Hunting for Human Infectious Agents at the Norwich Research Park (HHIAN)

GeCIP domain - Expression of interest

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

This proposed Prostate Cancer GeCIP will focus on several key areas:

1. Molecular stratification of localised disease deemed to be low risk to identify the poor prognostic subgroup of prostate cancer patients in this category. These studies are limited by the amount of tumour cells present in these samples but our groups have extensive expertise in MRI guided biopsies of these patients including saturation biopsies. Identifying the very small number of low risk patients that have a risk of disease progression is critically important to ensure that the majority of low risk prostate cancers are not over- treated. These studies will impact health care resource utilization by minimizing the overtreatment of indolent disease.
2. Elucidation of the molecular features of locally advanced high-risk patients in order to allow the molecular categorization of these cancers in order to distinguish good prognosis disease from those with poor prognosis disease to deliver the most appropriate treatment to each patient, minimizing risk of recurrence, delivering more precise treatment to each patient as well as decreasing overtreatment in lower risk disease. These studies will allow more precise treatment selection to higher risk patients.
3. Further study of the multi-focality of prostate cancer as well as the intra-patient heterogeneity of this disease, particularly comparing same patient localised and the lethal metastatic disease. These studies will also lead to an improved understanding of patient specific analyses of plasma tumour DNA and the study of tumour clone dynamics and treatment-related clonal evolution. Our groups already have major research commitments in this area.
4. Molecular stratification of lethal prostate cancer in order to deliver more precise cancer care to each patient, more efficient anti-cancer drug development, and improve outcome from this disease. We already have expertise in this domain and believe that this is critically important to not only current patient care but also future Phase III trial design. Studies ongoing with anticancer drugs targeting key genomic vulnerabilities in this disease can be linked to this GEL initiative if approved by this GeCIP's Steering Committee.
5. Establish a better understanding of primary and acquired resistance mechanisms associated with currently available anticancer treatments for this disease, including hormonal deprivation and tubulin drug treatment with the taxanes. These studies are critically important to determining better treatments for advanced prostate cancer.
6. Analysis of germline DNA in prostate cancer patients, particularly patients with high risk and lethal disease, with or without a family history of prostate cancer, to elucidate genomic variants that increase risk of prostate carcinogenesis. It is envisioned that such studies will impact the screening of selected individuals at high risk of getting clinically significant prostate cancer.

Proposed additional research activity including research activity focused on multi-omics and/or longitudinal data (as appropriate to domain):

Our group has major efforts ongoing utilizing genomic and transcriptomic data to drive the development of affordable and high throughput targeted next generation sequencing efforts that can be utilized today in routine patient care. We envision continuing to develop a prostate cancer

somatic cell gene biomarker suite of prognostic and predictive utility that can be broadly utilized in the NHS. Efforts to educate UK clinicians and pathologists on the utility of these data are also planned. Ongoing studies of serial plasma cell free DNA in our groups are also showing promise as response biomarkers and in efforts to understand drug resistance mechanisms and disease clonal evolution. We will also continue to focus on develop high performance genomic testing methods to identify patients at high risk of developing this disease. Efforts to molecularly interrogate circulating tumour cells are also ongoing.

Current funding and plans for procurement of funding for proposed research activities:
Selected investigators from the London Prostate Cancer Centre of Excellence are presented here due to lack of space.

Professor Johann de Bono

1. Stand up to Cancer (SU2C) A1100157 JS de Bono with The Prostate Cancer Foundation.
2. EuroCan FP7 305341 Circulating Tumor Cell TheRapeutic APheresis (CTCTRAP)
3. Department of Defense PC121152 "Targeting the Aberrant Androgen Receptor in Advanced Treatment-Resistant Prostate Cancer" 1/10/2013 – 1/10/2016 $356,910pa.
4. Prostate Cancer Foundation PCF-Movember Challenge Award. G Attard and JS de Bono Interrogating DNA Repair Defects to Improve Management of Advanced PCa.
5. Prostate Cancer Foundation Challenge Award. JS de Bono & Dr G Attard. Defining the clinical relevance of intratumor heterogeneity and subclonal evolution in prostate cancer.
6. Prostate Cancer UK. Grant Ref PG12-49. G Attard, de Bono JS (co-investigator). Using circulating plasma DNA as a multi-purpose biomarkers to identify aggressive prostate cancer and mechanisms of drug resistance.
7. C12540/A15573 Cancer Research UK Scientific Executive Board Experimental Cancer Medicine Centre Network award.
8. Prostate Cancer UK, Grant Ref. PG13-036, de Bono JS Lead Applicant. CHD1 Deletion: Implications to Prostate Cancer.
9. London Movember Prostate Cancer Centre, Ref. CEO13-2-002, de Bono J Director of Centre. Harnessing germline and tumour (tissue and plasma) genomic changes for targeted screening and more precise prostate cancer care.

Professor Ros Eeles

1. ERC-Adg-339208 (PI:Eeles) ERC FP7 BARCODE EUR 2,499,123 Oct 2014-Sep 2019
2. Prostate Cancer Trials (PI:Eeles) Bob Champion £100,000 Jun 2014 – Jul 2015
3. C5047/A17528 (PI:Eeles) CR-UK £2,162,200 Oct 2014-Sep 2019
4. Translational Studies in prostate cancer genetics: an oncogenetics programme
5. Centre of Excellence PCUK/Movember £283,471 Jul 2014–Jun 2019
6. (Joint PI:Eeles) PROFILE Study of targeted screening in men with a family history of prostate cancer
7. PG13 – 001(PI:Eeles) PCUK/Movember £200,703 Feb 2014-Jan 2017
8. Identification of DNA Repair gene mutations as a predisposition to early onset and aggressive prostate cancer.
9. GAP1 Funding Award (PI:Eeles) Movember £256,282 May 2013-Apr 2015 Integrated Global Serum Biomarker
10. C5047/A14835 (Joint PI: Eeles/Cooper) CR-UK £621,753 Sep 2011- Aug 2015
11. Full Project: (ICGC) International Cancer Genome Consortium: The Prostate Cancer Initiative.
12. THE IMPACT STUDY (PI:Eeles) CR-UK £419,529 Sep 2011-Aug 2015 Application for a multinational targeted prostate screening study based on genotype
13. THE IMPACT STUDY (PI:Eeles) The Ronald & Rita Mcaulay Foundation. £806,502 Apr 2011 – Mar 2015

14. THE IMPACT STUDY: Application for a multinational targeted prostate screening study based on genotype.

Professor Mark Emberton
Chief Investigator: MRC GBP 5.5M; Wellcome HICF GBP2.2M; PROMIS NIHR HTA GBP 2.4M; INDEX USHIFU USD 2.1M; HISTOSCAN EURO
0.5M; WST-11 Phase II Multi-centre Phase II EURO 0.8M; NCRI HIFU Hemi-ablation Phase I/II; NCRI HIFU Focal-ablation Phase I/II; NCRI HIFU Index-ablation Phase I/II; NCRI MAPPED GSK Investigator Led GBP 0.2M;

UK Principal Investigator: NIH, USA Tissue Type Imaging USD 3.6M

Dr Chris Parker
1. 1, STAMPEDE: trial of local radiotherapy to the prostate in men with metastatic disease. C. Parker (principal investigator) and STAMPEDE Trial Management Group. CRUK/MRC. £1,126,146 (2013-2017)
2. An evaluation of multi-functional MRI in the diagnosis and characterization of prostate cancer. M Emberton, C Parker, H Ahmed (co-principal applicants), A Padhani, R Gabe, M Parmar, M Sydes. NIHR HTA £2.3m (2011-2014)
3. RADICALS: Randomised phase III trial of adjuvant vs selective salvage treatment after radical prostatectomy for localised prostate cancer. C Parker, C Catton, C Morash, H Payne, JP Logue, MR Sydes, NW Clarke, HG Kynaston, JK Mellon, M Parmar. CTAAC (2007 to 2020) C7829/A6381. £117,237 in year 1.

Professor Charlotte Bevan
Prostate Cancer UK (Movember/PCUK Centre of Excellence, 3 project grants, 1 studentship, 1 pilot grant), Cancer Research UK (2 project grants, 2 studentships), Wellcome Trust (1 Clinical Research Fellowship),Johnson & Johnson/Janssen (1 project grant), Medical Research Council (1 project grant).

Dr Amanda Swain
1. Two Career Development Awards (NCRI South of England Prostate Cancer Research Collaborative and MRC) and was a coapplicant on a Centre Grant (PCUK Movember Centre of Excellence)
2. Obtained seven project grants to fund independent laboratory research and post doctoral fellow salaries. Funding bodies: Prostate Cancer UK (1 grant); International Fund Congenital Adrenal Hyperplasia (1 grant); Medical Research Council (2 grants); Cancer Research UK (2 grants); Biotechnology and Biological Sciences Research Council (BBSRC) (1 grant).

Opportunities for education and training:

1. Medical staff (senior and junior): We will continue to reach out to physicians and surgeons treating prostate cancer through national and international meetings, including the BUG and NCRI meetings, as well as ESMO, AACR, ASCO meetings. Several members of our team are very involved in organising these meetings, with Professor Johann de Bono being Chair for ESMO 2014 and Co-Chair for AACR 2015. We also have in place a regular programme of research meetings funded by the Movember Foundation, involving the Centres of Excellence that will continue to educate prostate cancer physicians and trainees. Some of our staff are also involved in the NCRI CHG trainee scheme called JING, which organises regular workshops to train junior clinical cancer researchers.

2. Paramedical staff: We will continue to endeavour to increase the number of paramedic staff aware of the need for genetic counselling focussing on training more staff to deal with the expected significant numbers of genomic incidental findings that these studies will generate. This will involve dedicated meetings and workshops through the BUG and our Movember funded meetings.
3. Patients: We will continue to focus on educating patients through local and national initiatives utilising open days for face to face meetings, as recently organised in London through the Movember Centre of Excellence programme, as well as through digital media, and when necessary with the appropriate approval of press releases, patient representative will continue to have a major input into the designing of our studies through the Royal Marsden/Patient Care Advisory Group.

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.*

Participant Name	Participant organisation name	Expertise
Dr Bissan Al-Lazikani	Institute of Cancer Research	Bioinformatics, chemo-informatics, established
Dr Gerhardt Attard	Institute of Cancer Research/ Royal	Prostate cancer biology, treatment of metastatic
Dr Elizabeth Bancroft	The Royal Marsden	Incidental findings in genome sequencing initiatives
Dr Julian Barwell	Leicestershire Clinical Genetics Department ,	Clinical genetics
Professor Daniel	Barts Health NHS Trust	Pathology
Professor Charlotte	Imperial College London	Androgen receptor signalling
Dr Gunther Boysen	Institute of Cancer Research	Prostate Cancer Biology; functional studies
Dr Daniel Simon Brewer	Norwich Medical School, Norwich Research	Bioinformatic studies of prostate cancer
Professor Bob Brown	Imperial College London	Epigenetic studies of cancer
Dr Suzanne Carreira	Institute of Cancer Research	Genomic analyses of prostate cancer and analyses of cell free
Dr Simon Chowdhury	Guy's and St Thomas' Hospital	Urological oncologist; treatment of metastatic
Professor Colin Cooper	Institute of Cancer Research and	Molecular biologist; interrogation of genomic
Dr Simon Crabb	Southampton General Hospital	Oncologist; systemic treatment of prostate cancer
Professor Johann de Bono	Institute of Cancer Research/ Royal Marsden	Clinician-scientist; treatment of metastatic prostate cancer and prostate cancer biology
Professor David Dearnaley	Institute of Cancer Research/ Royal	Oncologist; radiotherapy and systemic treatment of
Professor Ros Eeles	Institute of Cancer Research	Oncologist; prostate cancer genomics and hereditary prostate
Professor Mark	University College London	Urology, focal therapy for prostate
Dr John Frew	Northern Centre for Cancer Care Newcastle-	Clinical oncologist focused on treating prostate cancer.
Dr Emma Hall	Institute of Cancer Research	Statistics
Professor Freddie Hamdy	University of Oxford, Nuffield Dept. of Surgical Sciences	Management of urological malignancies, in particular
Dr Rob Jones	Beatson Institute, University of Glasgow	Oncologist. Metastatic Prostate Cancer NCRI Sub-

Dr Roger Kockelbergh	Leicester General Hospital	Urological oncologist
Dr Mark Linch	UCL Cancer Institute/ University College London Hospital	Uro-oncologist/Genomic and signalling heterogeneity in
Mr Ian Liston	Self employed	Patient Representative
Professor Malcolm Mason	Institute of Cancer & Genetics Cardiff University	Oncologist focused on treating prostate cancer. Prostate
Dr Daniel Nava Rodrigues	Institute of Cancer Research	Pathologist focused on molecular pathology of
Dr Sarwar Naveed	Charing Cross Hospital Department of Medical	Oncologist treating prostate cancer
Professor David Neal	University of Cambridge, Department of	Urological oncology including robotic prostatectomy and
Dr Simon Pacey	Addenbrooke's Hospital,	Oncologist; treatment of prostate
Dr Chris Parker	Royal Marsden	Treatment of prostate cancer
Dr Heather Payne	University College London Hospitals	Clinical Oncologist. Director of British Urological Cancer Group (BUG)
Dr Andrew Protheroe	Churchill Hospital Oxford	Systemic treatment of prostate
Dr Amanda Swain	Institute of Cancer Research	Genomics, transgenic models
Dr Nick Van Aas	The Royal Marsden	Oncologist treating prostate cancer
Dr Jan Hendrik Piet van der	London School of Hygiene and Tropical Medicine	Statistician
Peter van Loo	Cancer Research UK LRI	Bioinformatics
Professor David Waugh	Queen's University Belfast	Inflammation in the pathogenesis of prostate
Dr David Wedge	Wellcome Trust Sanger Institute Cambridge	Cancer genomics, subclonality and evolution in
Professor Theresa	Royal Marsden	Professor of cancer nursing
Dr Wei Yuan	Institute of Cancer Research	Bioinformatics

International collaborators and advisory committee:
Dr Arul Chinnaiyan, University of Michigan; Dr Levi Garraway Dana Farber and Broad Institute, Boston; Dr Scott Tomlins, University of Michigan Dr Mark Rubin, Weill Medical College, Cornell University; Dr Peter Nelson, Fred Hutchinson Cancer Research Centre; Dr Charles Sawyers, Memorial Sloan-Kettering Cancer Centre; Dr Howard Soule, Prostate Cancer Foundation; Dr Steve Bova, University of Tampere, BioMediTech, Tampere University Hospital; Dr Tapio Visakorpi, University of Tampere, BioMediTech, Tampere University Hospital.

Mechanisms for pre-competitive interaction with partners from industry:
Our group already has ongoing extensive collaborations with national and international partners in industry based in both the diagnostic and therapeutic domains. These include multiple interactions with Illumina, as well as an ongoing collaboration with Ion Torrent on plasma cell free DNA, and strong interactions with QIAGEN including a collaborative research agreement involving prostate cancer biomarker development. These collaborations have specifically focused on blood-based biomarkers including plasma DNA, circulating tumour cell genomic analyses and exosome analyses. We also have multiple established and broad collaborations with the Pharmaceutical industry, especially in the area of prostate cancer drug development with several members of our team having led multiple key drug registration trials including abiraterone, cabazitaxel, enzalutamide and radium 223. Our links involve most of the key large Pharma players focused on prostate cancer drug development including Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, GSK, Johnson & Johnson, Medivation, Pfizer, Roche/Genentech and Sanofi Aventis. We also have strong links and ongoing collaborations with many Biotech companies from not only the UK, such

as Astex Pharmaceuticals, but also North America, such as Clovis, and Japan such as Taiho. We envision that involvement in this Genomic England project will allow us to continue to successfully deliver the best therapeutic trials for prostate cancer patients, ensuring that the best and most important trials are also conducted in the UK, and also allowing the delivery of improvements in prostate cancer. Critically such studies are already allowing us to stratify sporadic metastatic prostate cancer through targeted next generation sequencing studies of key DNA repair genes allowing successful treatment with the PARP inhibitor olaparib in an innovative and adaptive clinical trial design called TO-PARP that incorporates exome and transcriptome sequencing of fresh biopsies from every metastatic castration resistant prostate cancer patient. The development of such innovative trial designs will be key to the optimal incorporation of genomic data into successful drug development, and elucidation of molecular stratification strategies.

Detailed research plan – Cancer Main Programme Gear 2 studies

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**PR01: Genetic analysis of markers of Prostate cancer severity in Afro-Caribbean men**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Afro-Caribbean men diagnosed with any stage of Prostate Cancer
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.*	We would like to collect 10-20 ml of blood for germline DNA analysis, and isolation of circulating tumour cells where present, plus biopsy tissue from primary and metastatic tumours (when present) at the time of diagnosis. We would like to recruit 100 Afro-Caribbean men with Prostate cancer
# cores per tumour (if multi-region biopsying proposed)	NA
Follow-up samples following first ascertainment	NA
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	Afro-Caribbean men have a two-three fold greater risk of developing prostate cancer than white or Asian men and their disease is more likely to be severe. The key objectives for this study are to identify genetic markers (i.e. SNPs, gene fusions) specific to prostate cancer severity in Afro- Caribbean men. We are already studying 4 SNPs related to the expression of Duffy antigen receptor for chemokines (DARC) in Afro Caribbean vs white men to determine whether the genotype of this is related to severe prostate cancer. It is known that in breast cancer, a genotype of DARC leading to a decreased expression on red blood cells (Duffy FES (erythrocyte silent)) which is present in upto 80% of Afro-Caribbean women – is associated with more severe breast cancer.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	Approximately 42% of the risk of developing Prostate cancer comes from inherited genetic factors: The risk of developing prostate cancer is increased two-fold among first-degree relatives of men with the disease. In Afro-Caribbean men, at least 12 SNPs found at chromosomes 8q24, 17q21, and 19q13.33 (the latter containing 3 SNPs associated with increased PSA expression in Afro-Caribbean men) have been identified (reviewed in (Eeles et al., 2014; McGinley et al., 2015). With our samples we could confirm expression of these SNPs and correlation to severe disease and also identify other SNPs and gene fusions in this cohort that correlate with severe Prostate cancer. Access to tumour tissue and circulating

	tumour cells could also allow WES (whole exomic sequencing) and RNA-seq to identify somatic mutations occurring in this cohort. Several epigenetic changes have also been described in prostate cancer and in methylation analyses, five genes (AR, RARbeta2, SPARC, TIMP3, and NKX2-5) have been found to be significantly more highly methylated in prostate cancer tissue samples from African-American men than from white men (P <0.05) . Therefore, it would also be desirable to study epigenetic modifications associated with severe disease in our cohort. **References** Eeles, R., C. Goh, E. Castro, E. Bancroft, M. Guy, A. A. A. Olama, D. Easton, and Z. Kote-Jarai, 2014, The genetic epidemiology of prostate cancer and its clinical implications, *Nat Rev Urol*, **11**(**1**), 18-31. McGinley, K. F., K. J. Tay, and J. W. Moul, 2015, Prostate cancer in men of African origin, *Nat Rev Urol*, **advance online publication**.
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?	We are already collecting blood and plasma samples for a clinical study to determine the association of DARC antigen status with prostate cancer severity in Afro-Caribbean men and have collected 40 blood samples so far from Afro-Caribbean men and 50 samples from Caucasian men. Co-recruitment to this other trial is optional.
Is this sub-study a new therapeutic trial?	No

Full proposal (total max 1500 words per Gear 2 Substudy)	
Title *(max 150 characters)*	**PR02: Interrogating genomic scars in whole genome sequencing data of tumours from the 100,000 genomes project.**
Cohort details and scientific case	
Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics)	Men diagnosed with any stage of Prostate Cancer
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.*	We would like to collect 10-20 ml of blood for germline DNA analysis, plus biopsy tissue from primary and metastatic tumours (when present) at the time of diagnosis.

# cores per tumour (if multi-region biopsying proposed)	NA
Follow-up samples following first ascertainment	NA
Purpose of analysis WGS and clinical data from this cohort of patients (brief)	Solid tumours such as prostate, breast, and ovarian or cancers are characterised by complex compositions of numerical and structural chromosomal DNA alterations obtained by multiple mutational processes occurring over the lifetime of a tumour. These alterations act as traceable genomic "scars" that have proven to be useful as both markers predictive of disease progression and tools to uncover the mechanisms underlying genomic alterations leading to the development of biomarkers of response to drugs that exploit the defects driving genomic instability. These genomic scars can also be attributed to germline mutations in the BRCA1 and BRCA2 familial cancer genes, the products of which are required for the reliable repair of DNA double-strand breaks by homologous recombination. While BRCA1 and BRCA2 account for some of the genomic instability within these tumours, for the majority, the causes and consequences of genomic instability are still to be determined.
Scientific case and insights that will be gained from this cohort (more details, as indicated)	We, the Cancer Bioinformatics group at King's College London, KCL (UK), have developed several different workflows to capture a suite of large-scale genomic aberrations and numerical chromosomal instability measures (Watkins et al., Cancer Discovery 2015). These genomic scars provide a granular description of the potential defects that may affect genomic integrity and have revealed certain patterns to be good indicators of sensitivity to drugs such as platinum salts or microtubule-stabilising agents. We, therefore, would like to investigate our set of genomic scars in the whole genome sequencing data from GeCIP and in particular interrogate the breakpoints at which these genomic patterns occur. By examining the sequence context and functional element enrichment of these breakpoints, we anticipate that will identify the mutational processes responsible for the generation of these patterns. Furthermore we will explore their clonal heterogeneity and prevalence, and relate them to prognosis.
Alignment to clinical trials	
Is it proposed that this sub-study is aligned to an existing clinical trial/sample collection study?	We are already collecting blood and plasma samples for a clinical study to determine the

Study details (incl Phase, commercial partner, geographic recruitment, remuneration). Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility?	association of DARC antigen status with prostate cancer severity in Afro-Caribbean men and have collected 40 blood samples so far from Afro-Caribbean men and 50 samples from Caucasian men. Co-recruitment to this other trial is optional.
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	Prostate cancer
Project title *(max 150 characters)*	**Prostate 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.