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

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

The domain has been formed with the following subdomains which allign with the objectives of the domain overall:

1. Interrogation of variants of unknown pathogenicity;
2. Tumour evolution;
3. Tumour heterogeneity/variability;
4. Circulating cancer biomarkers;
5. Pharmacogenomics;
6. Integrated functional biology;
7. Digital pathology image analysis and algorithm development

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)*

Testicular cancer is the commonest cancer and leading cause of death among young men, with >2000 UK cases annually and its frequency is increasing. Testicular cancer is caused by uncontrolled growth in the testes and can occur in any of the different anatomical parts of the organ. The most frequent type of tumour (accounting for about 95% of all testicular tumours) are those of the germ cells – germ cell tumours (GCTs). Although most patients have good clinical outcomes, those in the highest risk group still have only a 50:50 chance of surviving cancer, despite decades of clinical trials. Furthermore, current chemotherapy treatments have substantial toxicities. The Testicular Cancer GeCIP Domain want to take a 'pan-omics' approach to testicular cancer, that is using the wealth of data provided in the whole genome sequencing that will be produced by the 100,000 Genomes Project alongside all of the other research data available, to better identify the best treatments for each individual patient, and better identify the patients who have the highest long-term risk.

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

Lead Applicant(s)	
Name	Andrew Protheroe
Post	Consultant Uro-oncologist
Department	Oxford Cancer and Haematology Centre
Institution	Oxford University Hospitals NHS Foundation Trust
Current commercial links	

GeCIP domain - Expression of interest

Full proposal	
Title *(max 150 characters)*	**Testicular 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 and subdomains bring together NHS clinicians in oncology, pathology and researchers with genomic, bioinformatic and biological expertise, all at the very cutting edge of their respective fields. This has created a unique group of testicular cancer experts able to take the WGS data from the 100,000 Genomes project and use it to answer key (as yet) unanswered questions about this group of tumours. The Testis Cancer Domain now has the opportunity to fully understand the biology of this intriguing cancer and address unanswered biological and clinical questions. The domain will work to drive forward the translational aspects of WGS, ensuring that key findings are translated into real patient benefit.

Subdomain 1: Interrogation of variants of unknown pathogenicity (Taylor, Popitsch). Whilst the GEL analysis pipeline will investigate and return known pathogenic variants in established cancer genes for a given tumour type to the referring GMCs, it is likely that a host of variants of unknown significance will be generated.

Focus 1: investigate mutations in novel testis cancer genes and novel mutations in known cancer genes, in order to support patient diagnoses and treatment selection;

Focus 2: work with the interpretation, validation and feedback domain to update clinical reporting and data interpretation;

Focus 3: contribute to the development of policy on feedback for secondary (looked-for) findings to patients;

Focus 4: in due course, validate the clinical impact of variants of previously unknown significance

Subdomain 2: Tumour evolution (Berney, Verrill, Tomlinson, Turnbull). This subdomain will use innovative interpretation and study of the genetic architecture of testicular cancer to develop unique insights that will offer important translational potential.

Focus 1: study the evolution of testicular tumours to retroperitoneal or other metastatic disease sites, post chemotherapy changes and identification of lethal clones.

Focus 2: use knowledge of this genomic architecture to validate/characterise variants, identify novel therapeutic agents that may prevent the development of such clones and/or repurpose existing therapies.

Subdomain 3: Tumour heterogeneity/variability (Berney, Tomlinson, Verrill, Murray, Coleman, Amatruda, McNeish, Gershenson). GCTs are classified as seminoma or non-seminoma; the former group are the exemplar of exquisite cisplatin sensitivity, whilst the latter group are often composed of mixed malignant histological subtypes (yolk sac tumour, teratoma, embryonal carcinoma and choriocarcinoma) and can be associated with worse clinical outcomes in part through cisplatin resistance. Furthermore, GCTs are unique in arising from the neonatal period through to late adulthood, but with a peak in early adulthood (and age of presentation in adults

may be increasing); and arise at different anatomical sites (e.g. testis and ovary as well as extragonadal tumours).

Focus 1: evaluate coding and non-coding genomic variants/CNVs between and within seminoma and non-seminoma; to elucidate mechanisms or cisplatin sensitivity/resistance;

Focus 2: compare coding and non-coding genomic variants/CNVs across the spectrum of GCTs observed clinically: GCTS in adult versus paediatric patients; GCTs in male versus female patients; GCTs of the testis versus ovarian disease.

Subdomain 4: Circulating cancer biomarkers (Murray, Coleman, Litchfield, Turnbull, Huddart, Amatruda). Only 60% of GCT patients are serum AFP/HCG marker-positive, thus many patients rely on serial CT scans for disease-monitoring and follow-up, with associated radiation burden and potential second-cancer risk. Furthermore, no prognostic circulating markers exist, which would assist clinical decision making.

Focus 1: Correlation of coding genomic variants with circulating ctDNA profiles at diagnosis and during treatment and clinical outcome;

Focus 2: Correlation of non-coding genomic variants with circulating microRNA profiles at diagnosis and during treatment and clinical outcome;

Focus 3: Establish 'liquid biopsy' for routine clinical practice as direct or surrogate markers of WGS variants and clinical outcome.

Subdomain 5: Pharmacogenomics (Fairfax, Church, Protheroe). Testis cancer patients are usually treated with cisplatin, etoposide and bleomycin, which are associated with substantial toxicities. We urgently need to identify variants as markers of susceptibility to treatment toxicities and embed these into clinical practice to facilitate clinical decision making and personalised medicine. For example, genetic variants in TPMT and COMT (e.g. PMID 19898482), amongst others, have been associated with cisplatin ototoxicity. At present however, findings are commonly not reproducible between cohorts and this remains merely a research tool.

Focus 1: Confirm or refute TPMT, COMT, ACYP2 and ABCC3 as susceptibility variants for cisplatin ototoxicity, and identify other susceptibility variants for this risk;

Focus 2: Confirm or refute the homozygous variant G/G of the bleomycin hydrolase gene (BLMH) SNP A1450G as a marker of poor prognosis (PMID 18398146), and identify other susceptibility variants for this risk;

Focus 3: Identify other variants associated with treatment toxicities of therapy and develop methodologies to embed these tests into clinical practice to assist personalised medicine.

Subdomain 6: Integrated functional biology (Litchfield, Shipley, Turnbull, Murray, Coleman, Amatruda, Sweeney, Van Allen). We will identify the functional significance of coding and non-coding genomic variants, to assist the development of novel therapies, new clinical trials and personalised medicine.

Focus 1: integrate genomic variants with existing transcriptomic and proteomic data, linked to treatment responses and outcomes;

Focus 2: identify activity of cellular signalling pathways involved with different genomic variants and link to disease status, pathology and treatment response;

Focus 3: use such knowledge to inform parallel, complementary *in vitro* and *in vivo* studies of GCTs to identify new treatments for clinical testing and to overcome cisplatin resistance.

Subdomain 7: Digital pathology image analysis and algorithm development (Berney, Browning, Lundin, Verrill).

Focus 1: Digital image analysis of sequenced tumours using established and novel algorithms (classifiers) and machine learning;

Focus 2: Once established, embed such digital algorithms into routine clinical practice, to support clinical decision-making and clinical trials.

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

Role	Experience
Domain leads Andrew Protheroe andrew.protheroe@oncology.ox.ac.uk	NHS Consultant Oncologist specialising in Uro-oncology for fourteen years including testicular cancer. As lead Network oncologist for Testicular Cancer established the local supra-regional network in line with IOG guidance and hav been a member of the Testicular Cancer Clinical studies group for 2 years. Previously been a member of the Renal and Bladder cancer CSG's and a membe of the Bladder chemotherapy subgroup. Since 2014 he has been the co-clinical director for the NIHR Thames Valley and South Midlands Clinical Research Network (population 2.4 million) responsible for developing the infrastructure and facilitate NIHR portfolio research across the network, with a budget of approximately 14 million pounds. Established and run successfully a portfolio o studies in urological cancer locally, with national and international collaboratio Published over 60 peer-reviewed papers. Recently involved in an international consortium contributing data for outcomes in stage I testicular cancer. Set up testicular cancer database with over 1200 patients with complete dataset. Deputy chair of the TMG overseeing Southampton's Clinical trials unit, and a CTAAC reviewer. Principle investigator in over fifty predominantly phase II and III studies (a few phase I). Founding trustee of urological cancer charity (UCARE
Domain deputy Clare Verrill; Matthew Murray Clare.Verrill@ouh.nhs.uk; mjm16@cam.ac.uk	Senior Clinical Lecturer in Pathology and Honorary Consultant in Histopatholog specialising in urological pathology. Thames Valley supra-regional lead for germ cell tumour pathology, reviewing all regional germ cell tumours, mainly testicular, but also ovarian and extragonadal. International expert in testicular tumour pathology, speaking at the recent International Society of Urological Pathology testicular tumour consensus conference. Lead for Molecular Pathology in Oxford GMC. Involved in other whole genome sequencing initiatives e.g. Prostate International Cancer Genome Consortium (ICGC). Lead for digital pathology in Oxford, research includes image analysis and algorithm development in testicular germ cell tumours. Member of NCRI Testis Cancer CSG. University Lecturer and Honorary Consultant Paediatric Oncologist, specialising in molecular cancer research, particularly germ cell tumours. His pioneering work has led to establishment of a circulating nucleic acid panel for diagnosis and disease-monitoring suitable for all patients with malignant GCTs, regardles of age/site/subtype. National and international clinical and biological leadershi roles, including the NCRI Testis Cancer CSG and the highly productive Malignan Germ-Cell-Tumour International Collaborative (MaGIC). Dr Murray is Investigat on a portfolio of grants, including as co-PI on a $2.3m St.Baldrick's Foundation

	grant (2015-2020) to underpin upcoming international GCT clinical trials, focussing on whole-exome sequencing and circulating nucleic acids.
GMC representative Dr Clare Verrill	Lead for molecular pathology, Oxford GMC. Involved throughout BRC 100,000 Genomes pilot in Oxford, with optimisation of sample pathways for whole genome sequencing and co-wrote the molecular pathology SOPs for the main 100,000 Genomes programme. Took an active role in the application process for Oxford to become a GMC and now sits on the Oxford GMC steering committee. Human Tissue Act Designated Individual for University of Oxford licence 12217, under which the Oxford tissue samples for 100,000 Genomes are being collected and CI for Oxford Radcliffe Biobank, including management of biobank team who are consenting patients and collecting samples.
Patient representative Mr Vincent Wolverson	Testicular cancer survivor, having been diagnosed originally in 1989, received chemotherapy post surgery and further treatment in 2009. Founder member and current Chair of It's On The Ball, a Norwich based charity, which aims to raise awareness of Testicular Cancer, and support patients affected by the disease and their families. Developed local initiatives including conducting awareness events in the local community, educational establishments including the University of East Anglia, the Friends of the local Hospital, and various business groups. Developing links with other regional awareness and support groups throughout the UK. Member of the NCRI Testes CSG since November 2014.
Education and Training lead Dr Lisa Browning	Histopathologist specialising in Uropathology, and Honorary Senior Clinical lecturer in Pathology. Previously Clinical Lecturer in Cellular Pathology at the University of Oxford. Currently Head of School and Training Programme Director for Health Education Thames Valley School of Histopathology. Involved since the outset in the BRC 100 000 Genomes pilot in Oxford through role as a BRC pathologist. On the Royal College of Pathologists' subcommittee tasked with initiating delivery of training for histopathology trainees in molecular pathology nationally. Experience over ten years in setting up and organising education meetings nationally and locally. Currently undertaking a Postgraduate Certificate in Clinical Education.
Validation and Feedback representative Dr David Church	An Academy of Medical Sciences / Health Foundation Clinician Scientist Fellow and Honorary Consultant Medical Oncologist at the University of Oxford. His work focuses on the identification of novel prognostic and predictive genomic biomarkers in cancer and their translation into clinical practice. He is based at the Wellcome Trust Centre for Human Genetics, where he collaborates closely with Ian Tomlinson, and has international collaborators in the US, Netherlands and Switzerland. He has received awards from the AMS, CRUK, the British Skin Foundation and the Oxford Cancer research Centre totalling >£1M. He is a co-CI in the FOCUS-4 trial.
Other domain members	The Testis Cancer GeCIP has broad expertise and representation in the following areas, in particular through the NCRI Testis Cancer Clinical Studies Group and its established interactions with Clinical Research Networks, other CSGs managing germ cell tumours (at other anatomical sites/other patient ages), academia, industry partners and international collaborators: Medical and Clinical Oncology: Andrew Protheroe (Oxford), Jonathan Shamash (Barts), Robert Huddart (ICR), Johnathan Joffe (Leeds), Thomas Powles (Barts), Danish Mazhar (Camb). Paediatric Oncology and Teenage and Young Adult (TYA) Oncology: Matthew Murray (Camb), Sara Stoneham (UCLH), Dan Stark (Leeds). Gynaecologic Oncology: Ian McNeish (Glasgow); Domain also already extends to international collaboration with David Gershenson (MD Anderson, TX) - see below.

	Clinical trial Leadership: Jonathan Shamash (Barts), Johnathan Joffe (Leeds), Andrew Protheroe (Oxford), Robert Huddart (ICR), Danish Mazhar (Camb). Histopathology and Molecular Pathology: Clare Verrill (Oxford), Dan Berney (Barts), Nicholas Coleman (Cambridge), Lisa Browning (Oxford). Clinical Genetics: Ian Tomlinson (Oxford), Clare Turnbull (ICR). Genomics: Kevin Litchfield (ICR), Janet Shipley (ICR), Clare Turnbull (ICR), Robert Huddart (ICR), Matthew Murray (Camb), Nicholas Coleman (Camb), Jenny Taylor (Oxford), Clare Verrill (Oxford). WGS Variant Analysis and Interpretation: Jenny Taylor (Oxford), Niko Popitsch (Oxford). Descriptive and Functional Biology: Kevin Litchfield (ICR), Janet Shipley (ICR), Clare Turnbull (ICR), Dan Berney (Barts), Matthew Murray (Camb), Nicholas Coleman (Camb), Robert Huddart (ICR), David Church (Oxford), James Amatruda (Dallas). Bioinformatics: Matthew Murray* (Camb), Nicholas Coleman* (Camb). *Through established collaboration with Dr Anton Enright's group, European Bioinformatics Institute, Hinxton, Cambs. Circulating Cancer Biomarkers: Matthew Murray* (Camb), Nicholas Coleman* (Camb), Kevin Litchfield (ICR), Clare Turnbull (ICR), Robert Huddart (ICR), James Amatruda (Dallas). *Through established collaboration with AstraZeneca for circulating microRNA profiles. Murray/Coleman and Amatruda lab also have agreement for relevant support in establishing ctDNA studies in GCTs from Dr Nitzan Rosenfeld (CRUK-CRI, Cambridge) – see attached letter of support. Cancer Evolution: Ian Tomlinson (Oxford), Clare Turnbull (ICR). Training: Lisa Browning (Oxford), Kevin Litchfield (PhD student, ICR), Ben Fairfax (NCRI Testis CSG trainee, Oxford), Matthew Murray (Camb), Andrew Protheroe (Oxford), Clare Verrill (Oxford), Sara Stoneham (UCLH). Patient Advocacy: Vincent Wolverson (patient representative). In addition, the majority of Domain members work with local/national charities, many of whom are patient-based, e.g. Jonathan Shamash (Orchid), Thomas Powles (Orchid), Andrew Protheroe (UCARE), Dan Berney (Orchid), Johnathan Joffe and Dan Stark, (Laura Crane Trust), Matthew Murray and Nicholas Coleman (Laura Crane Trust, Max Williamson Fund).
Potential international collaborators	Already well established (e.g. see JCO 2015, PMID 26304902): 1) Christopher Sweeney and Eliezer Van Allen, DFCI, Boston, US – biology of testis cancer; involvement with TCGA testis cancer data: https://tcga-data.nci.nih.gov/tcga/ 2) James Amatruda, UT Southwestern, Dallas, US – biology of paediatric germ cell tumours, genomics, whole exome sequencing (WES) data, functional biology. 3) David Gershenson, MD Anderson, US – gynaecological oncology, with special interest in ovarian germ cell tumours, clinical trial leadership. 4) Johan Lundin, Finnish Institute of Molecular Medicine – expert in digital image analysis, machine learning and algorithms evaluating histological features. http://www.webmicroscope.net/

Our GECIP Domain has extensive experience in interactions in drug development and collaborations with the pharmaceutical industry. For example, Dr Murray and Professor Coleman (Cambridge) have a formal circulating nucleic acid biomarker programme established with AstraZeneca for GCTs. However, in general, developing studies/collaborations in testicular cancer has been challenging since the patient numbers, particularly in poorer prognosis groups and refractory/relapsed patients are small. The testis tumour GeCIP Domain will generate WGS data that offers new insights into cellular pathways active in this disease and thus new targets for novel therapies. This in turn will offer strong opportunities and a compelling rationale for collaboration with relevant pharmaceutical companies.

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	Testicular Cancer
Project title *(max 150 characters)*	**Testicular 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.