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 in January 2015. On the 18th June 2015 we invited the inaugurated GeCIP domains to develop more detailed research plans working closely with Genomics England. 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 needed 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. Some of you have requested a template for the research plan which we now provide herewith.

We are only expecting one research plan per domain and have designed this form to contain common features with funder application systems to minimise duplication of effort. Please do not hesitate to contact us if you need help or advice.

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 including:

- a cover letter (optional)
- CV(s) from any new domain members which you have not already supplied (required)
- other supporting documents as relevant (optional)

Genomics England Clinical Interpretation Partnership (GeCIP) Detailed Research Plan Form

Application Summary	
GeCIP domain name	**Neuroendocrine Tumour**
Project title *(max 150 characters)*	**Neuroendocrine Tumour Research in the 100,000 Genomes Project**

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

GeCIP Aims:

1. To extend the knowledge of genetic aberrations underlying neuroendocrine neoplasms (NENs).
2. To use Whole Genome Sequencing (WGS) data to better defined distinct and/or common patterns of genomic alterations of NENs.
3. To establish a sustainable database of annotated genomic variants and curated clinical information to further support research in this heterogeneous and rare group of cancers.
4. To define the biological role of those aberrations (their role in the development, progression and metastatic spread of NENs), as well as their prognostic significance by means of correlations with tumour pathological characteristics and patient outcomes.
5. To validate data already published in literature (e.g. Scarpa, A *et al*. Nature. 2017, 543(7643):65-71).
6. To facilitate the creation of a preferential channel for the circulation of genetic data on NENs with the aim to speed the use of this data in the clinical management of patients and the recruitment in precision-medicine clinical trials.

GeCIP Objectives:

1. To collect and sequence germline and tumour DNA from up to 150 patients with associated clinical data from NEN patients recruited through routine clinical care pathways.
2. To describe common patterns of genomic alterations of well and poorly differentiated NEN tumours independent of their anatomical origin.
3. To describe distinct patterns of genomic alterations between morphologically poorly and well-differentiated tumours; according to Ki67 and anatomical origin.
4. In the long-term, to develop novel prognostic biomarkers and potential predictive biomarkers for systemic treatments.
5. To identify mutational signatures common to NENs and gain further insights into the spectrum of tumour mutational burden in these tumours.
6. To identify novel germline variants that may predispose to NENs
7. To confirm the functional effect of appropriate variants using *in vitro* studies.

8. To incorporate and integrate epigenomic data to the WGS data.

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).*

Neuroendocrine neoplasms (NENs) are tumours arising from cells that form the endocrine and nervous systems. They occur mainly in the organs of the gut and in the lungs. Once considered a rare tumour entity, their incidence and prevalence rates are increasing. Most NENs are slow growing and patients survive a long time with their tumour but in some cases tumours can be aggressive and prognosis is poor. Despite ongoing research, there are still relatively few treatments for those with aggressive tumours.
There is, therefore, a need to better understand those genetic changes that cause tumours to behave in this way, resulting in improved diagnosis and treatment.

Technical summary. *Information from this summary may be displayed on a public facing website. Please include plans for methodology, including experimental design and expected outputs of the research. (max 500 words)*

We will sequence germline and tumour DNA from up to 150 patients with NENs of various subtypes. We will collect additional clinical information including tumour grade, functional status and response to treatment, to help further subgroup these patients for analysis. We will analyse WGS data using the standard Genomics England pipeline looking for novel somatic and germline variants, and patterns of copy number changes, tumour mutational burden and mutational signatures correlated with clinical characteristics and outcome. We will select novel variants for further analysis, using a previously reported algorithm used to identify variants in genes associated with hereditary endocrine diseases (Newey *et al.* 2017). We will assess the functional consequences of these variants using appropriate general and protein-specific methods in molecular and cellular biology including *in vitro* assays for protein expression, cellular localisation, cell cycle analysis (by flow cytometry), migration and apoptosis. We will also perform analysis of the epigenome, including methylation array, and circulating-tumour DNA (ctDNA) and integrate these with WGS data. We hope this work will enable us to better understand the genetic and epigenetic basis of NENs and identify new prognostic factors, biomarkers and therapeutic targets.

Expected start date	**July 2018**
Expected end date	**October 2020**

Lead Applicant(s)	
Name	Dr Christina Thirlwell
Post	Senior Lecturer and Consultant Medical Oncologist
Department	Research Department of Oncology
Institution	UCL Cancer Institute
Current commercial links	None

Administrative Support	
Name	None
Email	
Telephone	

Subdomain leads		
Name	**Subdomain**	**Institution**
Rajesh Thakker & Kate Lines	Inherited NENs	OCDEM – University of Oxford
Christodoulos Pipinikas	Sporadic NENs	UCL Cancer Institute

Detailed research plan

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	**Neuroendocrine Neoplasm Research in the 100,000 Genomes Project**

Importance. *Explain the need for research in this area, and the rationale for the research planned. Give sufficient details of other past and current research to show that the aims are scientifically justified. Please refer to the 100,000 Genomes Project acceptable use(s) that apply to the proposal (page 6).*

Neuroendocrine neoplasms (NENs) are malignancies mainly arising from the gastro-entero-pancreatic tract and lungs. Although rare, the incidence and prevalence of these malignancies have been rising. The majority of cases display a low malignant potential and favourable prognosis but NENs include a wide spectrum of neoplasms with variable biological behaviours and clinical outcomes, even within each World Health Organisation (WHO) subgroup [well-differentiated (WD)-grade (G)1, WD-G2, WD-G3 and poorly differentiated (PD)-G3].

This is clinically and genetically a heterogeneous group of tumours and there is an unmet need to better understand the biology of NENs and their underlying genetic alterations. It is hoped that improved knowledge in this area will lead to identification of new biomarkers and targets for molecular imaging and therapeutics. This in turn, could improve patient outcomes, with new treatments for those with advanced/metastatic neoplasms and subgroups with poorest prognosis.

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.*

In order to achieve our objectives we will undertake a number of parallel workstreams:

Workstream 1: Collation of WGS data for patients already recruited

Patients with neuroendocrine tumours recruited, sequenced and analysed through other GeCIPs have already been identified (~50 patients) and we will work with Genomics England to have the raw sequencing data for these patients repatriated to the NEN GeCIP for analysis within the research environment.

Commented [SW1]: These genomes will remain organised under their original domains. Dr Thirlwell has contacted the relevant domain leads to request collaboration and ask for permission for the publication moratorium period be waved for the NET genomes.

Workstream 2: Accelerated recruitment

In order to facilitate accelerated recruitment prior the close of the project and obtain a cohort from which we can generate clinically meaningful data, we will contact specialist centres treating neuroendocrine tumours and ask them to encourage their patients to participate. We will also aim to recruit patients from the Royal Free Hospital Neuroendocrine Tumour (NET) Biobank and other UK ENETS Centres of Excellence including Oxford University Hospitals, Kings College Hospital, The Christie Hospital and Wessex NET Group. These will be patients who have had fresh frozen tissue collected after 2015 and who are alive and willing to provide consent and blood sample for germline analysis.

Workstream 3: Collection of extended clinical data

Given that NETs are a rare and heterogeneous group of tumours, we will ask recruiting centres to collect an extended panel of anonymised information on patients recruited with NENs, in order to facilitate more meaningful analysis. This will be collated by the GeCIP through direct contact with treating centres for upload by Genomics England to the research environment.

Information regarding patient demographics (gender, age, ethnicity, performance status) and clinical-pathological data (date of diagnosis, clinical presentation, resection margins, systemic treatments if any, tumour morphology and grading, TNM staging (ENETS/WHO), nodal status, Ki67, necrosis, mitoses, functionality, CgA, 5HIAA, hormone secreted (if functional)) will be collected by clinicians at the time of consent signature and from local medical records. This will be done retrospectively for patients already recruited.

Due to the nature of the project and the time scope, it is not expected to find multiple cases with systemic treatments. However, in these particular cases, the line of treatment, the Response Evaluation Criteria In Solid Tumours (RECIST), the progression status of each line and the date of progression should be recorded. These data will be used for correlations with the results of genetic analyses. Reference clinicians will be identified at each centre participating in the GeCIP project and will be responsible for the coordination of data collection at a local level.

Workstream 4: Analysis of WGS data

Following on from the Genomics England core pipeline, the NEN GeCIP will augment this rich dataset using additional methods and algorithms. Genomics England will check the integrity of the delivered data and confirm that it meets the required quality level. Initial alignment and calling of SNVs, indel, CNVs, tumour mutational burden and mutational signatures will utilise the Genomics England analysis pipeline for this.

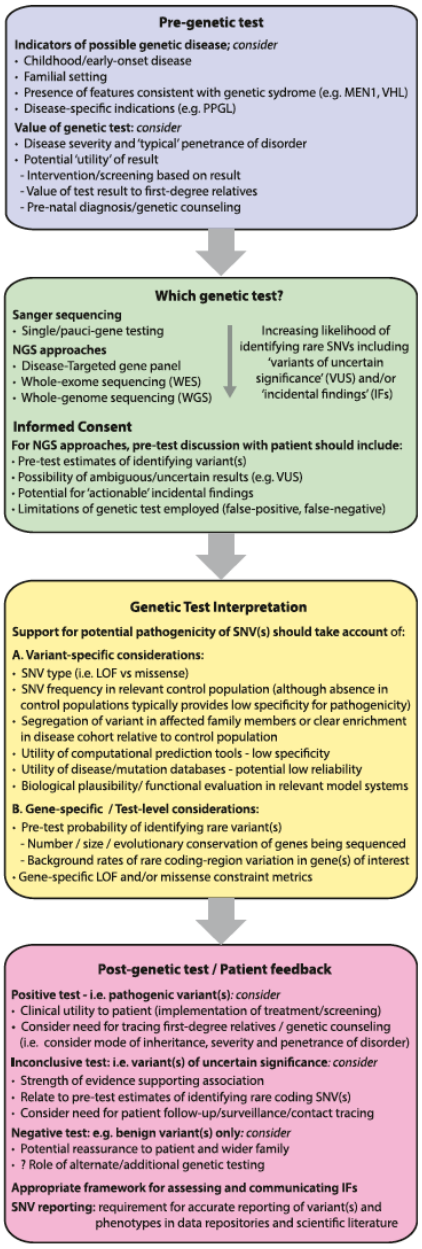
Bioinformatics support will be provided by both the Colorectal Cancer GeCIP bioinformatics team, and Jenny Taylor and Alistair Pagnamenta from the Wellcome Trust Centre for Human Genetics in Oxford with which NET GeCIP members already have established collaborations. We plan to primarily use bioinformatics tools listed within List_of_Embassy_apps.xlsx. However, we wish to retain the option to import other tools as required to meet the demands of subsequent data analysis including identification of low frequency variants and potential novel germline variants. We may wish to import BAM files and VCF files generated from WES or WGS of relevant patient cohorts to meta-analyse data, including epigenetic data.

The challenge with large scale sequencing data is determining which variants are pathogenic. The NET GeCIP will select novel NEN variants for further analysis, using our previously reported algorithm (Figure 1) to identify variants in genes associated with hereditary endocrine diseases (Newey *et al,* 2017). Approximately 20% of all NENs are due to hereditary syndromes, with at least 24 genes implicated in driving NEN tumourigenesis. Recent work by Scarpa and colleagues (2017) showed that 17% of pancreatic NENs have germline mutations in well characterised genes such as *Menin, VHL, MUTYH* and *BRCA2* which can be easily screened for using next generation sequencing panels. Many of the genes known to be associated with hereditary syndromes are also mutated in sporadic NENs, for example >40% of pancreatic NENs have a mutation in the MEN1 gene, that causes multiple endocrine neoplasia type 1, in which patients develop NENs predominantly in the pituitary, parathyroid and pancreas. Our algorithm takes into account the frequency, evolutionary

Commented [SW2]: This has been discussed with the Clinical data and Research Environment teams and is feasible.

conservation, segregation and predicted functional effects of the variant, and therefore, will be applicable to variants occurring in hereditary and sporadic NENs.

Figure 1:



Newey, P. J. et al. Journal of the Endocrine Society. 2017;1:1507.

Workstream 5: To analyse function effects of variants

The functional consequences of these variants, and therefore specific studies, will depend on the role of the encoded protein/product. We will analyse these using appropriate general and protein-specific methods in molecular and cellular biology, in which we have extensive experience. All of our studies will utilise mammalian cells (e.g. HEK293 or BON-1 cells) transfected with wild-type or mutant constructs, cells stably-expressing wild-type or mutant proteins, cells modified using RNA interference (RNAi) to reduce expression of encoded proteins, and tumour and normal cells from patients and mutant mice. General methods will include appropriate *in vitro* assays for: protein expression; cellular localisation (utilising specific antibodies, or tagged proteins); and tumour-related functions [e.g. proliferation (CellTiter Blue cell viability assay), cell cycle analysis (flow cytometry), colony formation (crystal violet staining), migration (transwell migration assay) and apoptosis (CaspaseGlo assays)], as described by our previous studies. We will also use these cells for protein-specific assays as illustrated by our studies of G-protein coupled receptors (GPCRs) e.g. the calcium-sensing receptor (CaSR), G-proteins, cytokine receptors, channels/transporters, transcription factors, and enzymes. Once the pathogenic function of the gene/protein is identified, we will also explore the use of potential therapeutic agents/drugs as illustrated by our work establishing roles for epigenetic modifiers, somatostatin analogues, gene therapy, calcimimetics and calcilytics.

Workstream 6: ctDNA analysis

A number of patients will have had plasma for circulating tumour DNA (ctDNA) collected as part of the project. For these samples, we would either perform WGS within one of the GeCIP's research groups or analyse the results following sequencing by Illumina through the core Genomics England infrastructure. We would use the same core analysis pipeline as discussed for WGS data, taking into account the need for comparison with tumour sequence and the fact that intra- (and possibly inter-) tumoural heterogeneity may be reflected in the ctDNA. From this work it will be possible to gain insights into the mutational spectrum of NETs, and develop non-invasive diagnostics and biomarkers.

Workstream 7: Methylome analysis

NENs are known to exhibit significant epigenetic dysregulation. Therefore, for samples with sufficient quality/quantity DNA and tumour purity we would aim to perform analysis of the epigenome. We will undertake genome-wide DNA methylation profiling using the Illumina EPIC array. Results will be analysed using the ChAMP2 pipeline in the R environment. We will then correlate methylation with WGS data in order to give novel insights into pathogenesis. In addition we may investigate the regulome and chromatin modifications using techniques including, but not limited to, ChIP-Seq and ATAC-Seq. We appreciate that a separate research proposal would be required for access to DNA samples for this work.

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.*

To-date, neuroendocrine tumours have been collected under a number of other GeCIPs subdomains, including Endocrine and Metabolism and Inherited Cancer Predisposition within the Rare Disease arm, Lung, Colorectal, Upper GI / HPB and Carcinoma of Unknown Primary within the Cancer arm. We will work closely with these GeCIPs to utilise these data and carry out further

analysis. In order to facilitate analysis of methylation data for NENs, we will collaborate with the Machine Learning GeCIP. We will also collaborate with the Colorectal Cancer GeCIP for bioinformatics support.

We will facilitate patient engagement through existing links with the NET Patient Foundation and the Association for Multiple Endocrine Neoplasia Disorders (AMEND).

We have existing collaborations with a large number of academic institutions affiliated with the GeCIP including University College London, University of Oxford and University of Manchester. We will feedback to the research committee of UK and Ireland Neuroendocrine Tumour Society (UKINETs).

Training. *Describe the planned involvement of trainees in the research and any specific training that will form part of your plan.*

The NET GeCIP has three medical oncology specialist trainees actively involved. Alison Berner, an ST4 academic clinical fellow at UCL Cancer Institute researching NENs of unknown primary. She has been involved in the drafting of this application and will be both consenting patients to the study at Royal Free Hospital and assisting with data analysis. She also has an honorary contract with Genomics England and is involved in the wider dissemination of 100,000 Genomes Project. Melissa Frizziero is a clinical research fellow in the NET/HPB group at The Christie NHS Foundation Trust, Manchester. She will be working alongside Dr Jorge Barriuso to set up and coordinate tumour sample and clinical data collection from NET patients referred/treated in Manchester. She will be also consenting patients to the study and collecting clinical information. She has contributed to the drafting of the application. Kate Young is a clinical research fellow and medical oncology trainee at the Royal Marsden and ICR. She is actively contributing to the GeCIP's research plan and will use the data generated as part of her translational research in pancreatic NET.

Other trainees from collaborating centres will be invited to be involved and provided with training. We plan to provide training in consent for the project to all staff recruiting patients with NENs. We will also provide access to training resources on cancer genomics via the South London GMC training website.

People and track record. *Explain why the group is well qualified to do this research, how the investigators would work together.*

Dr Christina Thirlwell is a Senior Lecturer at the UCL Cancer Institute. She is the Chair of the UKINETs Research Committee. She has an international reputation for undertaking integrated genomic analysis in NETs, sitting on national and international committees. Using an integrated approach combining genomic, epigenomic and transcriptomic data, her group have previously investigated neuroendocrine tumours of the pancreas and gastrointestinal tract (Pipinikas *et al*., 2015; Karpathakis *et al*., 2016; Karpathakis *et al*., 2017). These studies have provided clear evidence that these tumours are highly epigenetically dysregulated and have identified several altered biological pathways and genes that may form the basis for the development of novel therapeutic targets. Dr Thirlwell also leads the NET multidisciplinary clinic at Royal Free Hospital ENETS Centre of Excellence and is actively recruiting patients to trials.

Dr Christodoulos Pipinikas moved to UCL to work as a Research Associate in the Centre for Respiratory Research. During this post, he worked towards understanding the epigenetic changes associated with the progression of pre-invasive lung squamous cell carcinoma lesions into invasive cancer. In 2014, he joined UCL's Cancer Institute to work on pancreatic neuroendocrine tumours

Commented [SW3]: Please see comment 1.

(PanNETs) with the Clinical Epigenetics group. Using integrated approaches such as DNA methylation, exome and RNA sequencing, he is currently working towards understanding the genetic and epigenetic mechanisms associated with lung NET development and progression in order to identify better classification/prognostic tools and novel therapeutic targets. He is an active member of UKINETs and ENETS. In 2016, he was awarded a NET Patient Foundation Award and in 2018 with the ENETS CoE Excellence Academy Fellowship. As part of his affiliation to Royal Free Hospital (an ENETS Centre of Excellence), he is giving regular talks on the molecular/genetic aspects of NETs. Over the last few years, he has developed a particular interest in studying neuroendocrine tumours using integrated approaches and has established several national and international collaborations.

Prof Rajesh Thakker leads the Academic Endocrine Unit at University of Oxford, a group of basic and clinical scientists investigating the genetic, molecular and physiological basis of endocrine disorders that affect calcium homeostasis, and endocrine tumour development. By identifying and understanding the underlying mechanisms, they aim to establish better diagnostic methods and develop novel targeted therapies for these disorders to improve patient care. Their current key areas of research include the function of *Menin* and its putative role in epigenetic regulation, studies of *MEN1* gene-replacement therapy and epigenetic modifying drugs in NETs, and calcium-sensing by a G-protein coupled receptor signalling and trafficking. The group has a track record of investigating the pathophysiology of human diseases and have carried out molecular, cellular, and physiological analyses of more than 15 disorders, with identification of their defective genes and functional studies that explain the disease phenotypes.

Dr Kate Lines is a postdoctoral researcher within the Academic Endocrine Unit at University of Oxford. Her research focuses on understanding the epigenetic mechanisms causing tumour development in neuroendocrine tissues, and using this information to develop new diagnostic approaches and therapies. There is a key focus on pancreatic neuroendocrine tumours, particularly those caused by loss of the tumour suppressor protein menin. She is currently investigating compounds that inhibit epigenetic modifying proteins to determine their efficacy at reducing tumour cell proliferation in vitro, and tumour growth in vivo, with the aim of taking successful candidates into patients. She is also examining microRNA (miRNA) expression and regulation in neuroendocrine tumours including studying the potential use of miRNAs as tumour biomarkers.

Manchester European Neuroendocrine Tumour Society (ENETS) Centre of Excellence (CoE) was awarded CoE Excellence Status in 2011 for its work in clinical trials, basic and translational research of NETs. It is lead by Prof Juan Valle and two of its members are part of the GeCIP. Dr Jorge Barriuso completed his residency program in Medical Oncology at Hospital Universitario La Paz (Madrid, Spain) in 2005. Then, he obtained a “Rio Hortega” junior research contract and presented his PhD in May 2007. He has a special interest in gastro-intestinal malignancies, neuroendocrine tumours and drug development. In 2013, he moved to the University of Manchester to build new animal models in NETS and being involved in clinical research at The Christie ENETS Centre of Excellence with an ERC Marie-Curie Intra-European Fellowship. Dr Barriuso has published more than 60 peer-reviewed articles and 14 being in the NET field. In 2015 he was awarded with the TRANSNET grant of the UKINETS and in 2017 he received the ENETS CoE Fellowship Grant award. He works alongside Melissa Frizziero, a medical oncology specialist and clinical research fellow at the Christie ENETS CoE. She leads a number of clinical projects in in mixed adeno-neuroendocrine carcinoma and poorly differentiated neuroendocrine carcinoma and was awarded the 2018 ENETS Centre of Excellence Young Investigator Grant; a year lab-based fellowship to work on a translational project entitled “development of an alternative ‘precision medicine’ platform for identifying and testing

novel therapeutic strategies for advanced extra-pulmonary (EP), poorly differentiated (PD), neuroendocrine carcinoma (NEC)".

Dr Mohid Khan has over 10 years' experience in NETs as a gastroenterologist and is an active member of UKINETS and the NCRI NET subgroup. Having worked at the Royal Free, UCL and Royal Marsden, he moved to Cardiff in 2014 where he has led the development of the Wales NET Service across 15 hospitals commissioned by the Welsh government, co-produced with patients. His research in circulating tumour cells in NETs received a number of national and international awards and he has authored numerous publications on NETs in peer-reviewed journals. He has collaborated and led projects with a number of NET centres across Europe, and is a regular speaker at various forums. His work on quality of life, patient reported outcome measures and patient advocacy in NETs has received wide attention amongst patient communities and continues to work on media and health innovation projects in NETs whilst continuing to see patients in Wales's first dedicated NET clinic.

Dr Judith Cave is a Consultant Medical Oncologist and NET at University of Southampton Hospitals. She also leads the Wessex NET Group, an ENETS centre of excellence based across three sites (Dorset, Southampton and Portsmouth). They have a particular interest in surgical and liver directed treatment for NETS. They have a well-established tumour bank and a research program building on this, including a recently initiated study of the immune environment in NETS.

Dr Raj Srirajaskanthan is a Consultant in Gastroenterology and Neuroendocrine Tumours at the Kings Health Partners ENETS Centre of Excellence. The Kings College Hospital NET service has been running for over 30 years and in 2012 created the Kings Health Partners, Hampshire Hospital and Kent Oncology ENETS Centre of Excellence. The service covers a population of around 4-5 million. Over 2000 patients with NETS have been managed through this centre and currently they receive greater than 200 new referrals a year. They have an academic research programme with a focus on personalise medicine, quality of life and improved patient outcomes. A large number of patients are consented for use of the tissue biobank and they have been recruiting patients for the 100k genome project under the rare diseases and cancer; as part of the South London GMC.

Dr Kate Young is a clinical research fellow undertaking an MD(Res.) at the Royal Marsden and ICR, involving a translational study in pancreatic neuroendocrine tumours. She works in Dr Anguraj Sadanandam's lab at the ICR with an interest in the molecular subtyping and the immune landscape of pancreatic NETs. The lab is primarily focused on understanding intra- and inter-tumoural heterogeneity in pancreatic adenocarcinoma and NETs using cutting-edge computational methods and further exploring the mechanisms using wet-lab techniques. Dr Sadanandam is an expert in biomarker discovery and developing robust clinical biomarker assays. The gastrointestinal team at the Royal Marsden have an active NET service with a specialist NET MDT.

Associate Prof Jenny Taylor directs the Oxford Biomedical Research Centre – Genomic Medicine Theme and Dr Alistair Pagnamenta is a post-doctoral researcher within this group. The Genomic Medicine Theme aims to apply next-generation sequencing technologies (NGS) to the discovery of novel disease gene, evaluate and develop these technologies for rapid translation into the clinic, resulting in new NHS-based genetics services, and provide genetics and genomics infrastructure (platforms and expertise) to support other translational research projects. They already collaborate closely with the Academic Endocrine Unit at University of Oxford and have agreed to provide bioinformatics support for the GeCIP.

Initial analyses of the patient cohort would be undertaken collaboratively between GeCIP members with the aim of a joint publication of results. Depending on initial findings, projects including

validation of therapeutic targets or deeper analyses of individual tumour subtypes would then be allocated within the GeCIP according to interest and expertise of individual centres.

Clinical interpretation. *(Where relevant to your GeCIP) Describe your plans to ensure patient benefit through clinical interpretation relevant to your domain. This should specifically address variant interpretation and feedback and your interaction with the cross-cutting Validation and Feedback domain.*

Patient reports from initial analyses of tumours through the Genomics England pipeline for variant interpretation are already being sent to individual GMCs and recruiting hospitals via the Genomics England Interpretation Portal. These are discussed at local Genomic MDTs with results fed back to treating clinicians, who in turn, discuss these with patients.

Where analysis by our GeCIP results in the identification of a novel germline variant which is potentially disease causing, or a somatic variant that is potentially clinically actionable, we will discuss with the Validation and Feedback domain to ensure we have undertaken the appropriate validation. If this is the case, the result will be passed onto Genomics England in order that an updated genome report can be issued for the patient, which can be distributed to the GMC, along with any information on how to further clinically validate the result for the patient. Again, the treating clinician can then be notified via the Genomic MDT to inform the patient and arrange clinical genetics review as appropriate.

Beneficiaries. *How will the research benefit patients and healthcare institutions including the NHS, other researchers in the field? Are there other likely beneficiaries?*

This research has the potential to find novel disease-causing variants and confirm previously established patterns of genetic aberrations in NENs. This will benefit patients by facilitating better prognostication and subtyping, and identifying biomarkers and therapeutic targets.

As with any rare disease, collaborations at national level are vitally important and we would expect the infrastructure for our research will improve dissemination of knowledge between academic and healthcare institutions, with the potential for new translational studies and improved recruitment of patients to trials. Patients will continue to benefit well beyond the end of the project.

Commercial exploitation. *(Where relevant to your GeCIP) Genomics England has a very explicit intellectual property policy. We and other funders need to know if the proposed research likely to generate commercially exploitable results. Do you have commercial partners in place?*

We have no commercial partners.

References. *Provide key references related to the research you set out.*

1. Dasari, A et al. JAMA oncol 2017;3(10):1335-1342.
2. Bosman, T et al. 2010, Lyon, France: International Agency for Research on Cancer (IARC) Press.
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8. Strosberg, J et al. N Engl J Med. 2017;376(2):125-135.
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14. Reed, A. A. et al. American journal of physiology. Renal physiology. 2010;298:F365.
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16. Pearce, S. H. et al. N Engl J Med. 1996;335:1115.
17. Babinsky, V. N. et al. The Journal of biological chemistry. 2016;291:10876.
18. Karpathakis, A. et al. Clin Cancer Res. 2016;22(1):250-8
19. Pipinikas, C. et al. Endocr Relat Cancer. 2015;22(3):L13-8.

Data 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.

Omics samples

Analysis of omics samples. *Summarise any analyses that you are planning using omics samples taken as part of the Project. (max 300 words)*

We plan to perform epigenetic analysis and utilise WGS of ctDNA samples where available as discussed above in the main research plan.

Data access and security	
GeCIP domain name	**Neuroendocrine Tumours**
Project title *(max 150 characters)*	**Neuroendocrine Neoplasm 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 in the 'Importance' section (page 3).*

- ☑ *Clinical care*
- ☑ *Clinical trials feasibility*
- ☑ *Deeper phenotyping*
- ☑ *Education and training of health and public health professionals*
- ☑ *Hypothesis driven research and development in health and social care - observational*
- ☑ *Hypothesis driven research and development in health and social care - interventional*
- ☑ *Interpretation and validation of the Genomics England Knowledge Base*
- ☑ *Non hypothesis driven R&D - health*
- ☑ *Non hypothesis driven R&D - non health*
- ☑ *Other health use - clinical audit*
- ☑ *Public health purposes*
- ☑ *Subject access request*
- ☑ *Tool evaluation and improvement*

Information Governance

☑ The lead and sub-leads of this domain will read and signed the Information Governance Declaration form provided by Genomics England and will submit by e-mail signed copies to Genomics England alongside this research plan.

Any individual who wishes to access data under your embassy will be required to read and sign this for also. Access will only be granted to said individuals when a signed form has been processed and any other vetting processes detailed by Genomics England are completed.

Other attachments

Attach other documents in support of your application here including:

- a cover letter (optional)
- CV(s) from any new domain members which you have not already supplied (required)
- other supporting documents as relevant (optional)