# 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 | |
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| **GeCIP domain name** | **Cancer of Unknown Primary (CUP)** |
| **Project title** *(max 150 characters)* | **Cancer of unknown primary: research in the 100,000 Genomes Project** |

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

1. Elucidate key genomic pathways and drivers in metastatic phenotypes;
2. Investigate intra- and inter-tumour heterogeneity;
3. Assess and catalogue expression diagnostic classifiers;
4. Cross-compare '-omics' signatures with other metastatic tumour types

**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)*

Cancer of unknown primary (CUP) is a term that is used to describe cancer where the original (first) tumour, called the primary, cannot be found but only the metastatic tumours - the tumours that grow as the cancer spreads through the body are detectable. It might not be possible to identify the primary as 1) it may be too small to see on a scan, 2) it might have been attacked and killed by the immune system or 3) it might have "sloughed" off (as can happen in gut tumours), or 4) the types of cells found in the secondary tumours don't look like they've come from any obvious primary site. Despite an improvement in diagnostic techniques there has only been a small decline in mortality from CUP over the last six years, and only about 1 in 3 patients diagnosed with CUP will survive beyond a year. The Cancer of Unknown Primary GeCIP Domain will use the data from the 100,000 Genomes Project to define the changes in the tumour DNA, and try to identify factors that can be used to more accurately diagnose and understand CUP biology.

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

| Lead Applicant(s) | |
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| **Name** | Harpreet Wasan |
| **Post** | Consultant and Reader in Medical Oncology |
| **Department** | Department of Cancer Medicine |
| **Institution** | Imperial College Healthcare NHS Trust |
| **Current commercial links** | - Within the UK CUP-ONE trial we have developed links with 2 commercial testing partners for expression classifiers (Biotheranostics and Healthscope).<br>- I am discussing a possible CUP FFPE pilot with Thermofisher Scientific on their transcriptome (gene- and exon-level analysis of coding and ncRNA isoforms) Clarion-D assay system<br>- I have also been approached by both ROCHE and Foundation medicine to discuss CUP studies (but this has not yet happened as of Feb 2017) |

| Gear 2 Substudies |
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| **CP01: Development of a combined genomic diagnostic expression classifier and mutational genomic signature for CUP** |
| **CP02: Is it feasible to obtain genomic diagnostic expression classifier and mutational genomic signature for CUP with liquid biopsies.** |
| **CP03: Comparing the combined genomic diagnostic expression classifier and mutational genomic signature for CUP, in tumours defined as GI or lung across the relevant respective GeCIP domains (i.e. CRC, Upper GI and lung)** |

## GeCIP domain - Expression of interest

| Full proposal | |
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| **Title** *(max 150 characters)* | **Cancer of unknown primary 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.*

The overall aim is to define the somatic molecular changes in CUP at their highest current feasible level through the Genomics England 100,000 genomes project. There is a unique opportunity in CUP (unlike any other tumour type) to combine and extend the diagnostic CUP-ONE (a CRUK-funded trial) data within this GeCIP application, so that tissue samples provide coupled information on tissue of origin (through expression classifiers) and somatic genetics. CUP-ONE is currently being analysed and three expression classifiers are being directly compared for their correlation to the clinical scenarios and outcomes. We should by the end of 2017 / early 2018 have enough information from CUP-ONE to then apply and cross-correlate the best classifier (from CUP-ONE), and extend and refine this from the 100K samples collected. Furthermore the project can assess whether this combination is also assessable in liquid biopsies (cfDNA). The uniqueness of CUP is at many levels and the logistics of tissue collection and subsequent "omic" analyses should be of high parallel importance.

Specifically in CUP:

1. The highly metastatic phenotype (as patients usually present with > 6 metastases at diverse sites) should lead to the understanding of key metastatic (as opposed to general cancer) pathways and drivers. By definition all biopsies will be metastatic.
2. Related to this, intra- and inter-tumour heterogeneity should be at the highest complexity in CUP compared to site specific tumours, allowing an opportunity to study this in the context of defining the logistics and process and QA of small biopsy collection. Where consent is given, multiple biopsies (at least 2-3) should be safe and feasible, including from different targets or organs. The CUP-ONE trial demonstrated that most centres were successful at taking 2 core biopsies and cytology (FNA) was not allowed.
3. A unique opportunity to assess and catalogue expression diagnostic classifiers, which may be faster and more consistent to achieve than current manual pathological techniques with immunohistochemistry. A combined genomic approach to ascertaining the molecular diagnostic and cancer landscape of the tumour may well be quicker, easier and cheaper than a standard current complex diagnostic work-up, including multiple imaging modalities "in search of" the elusive primary.
4. Repeat post-treatment biopsies (with appropriate consents). In CUP-ONE we demonstrated in a pilot sub-study that about 10% of the patients were exceptional responders and alive beyond 18 months. (Wasan HS, J. Paul, M.C. Nicolson et al Ann Oncol (2014) 25 (suppl 4): iv397. doi: 10.1093/ annonc /mdu345.8 ).
5. QOL and health economics data collection. This has also been assessed in CUP-ONE. We have worked with The CUP Foundation, who have funded researchers at the university of Southampton for psychological studies of CUP patients. In addition the proposed lead (Wasan HS) is a co-applicant in the current Australian Study (SUPER: Solving Unknown Primary cancER), which have and are developing tools that might better assess this sensitively in a way that is meaningful to patients with one of its co-primary aims being a comprehensive psychosocial analysis of CUP Patients. (2015. Experiences of Care of Patients with Cancer of Unknown Primary (CUP): Analysis of the 2010, 2011-12 & 2013 Cancer Patient Experience Survey. Wagland R, Bracher M, Ibanez Esqueda A, Schofield P,

Richardson A. Southampton University, Health Sciences. 2013. Uncertainty and anxiety in the cancer of unknown primary patient journey: a multiperspective qualitative study. A Richardson, R Wagland, R Foster, J Symons, C Davis, L Boyland,C Foster, J Addington-Hall in BMJ_Support_Palliat_Care-2013 (November))

6. Early engagement with industry and pharms partners to achieve an ethical and affordable treatment options model and network for the patients undergoing genomic sequencing in the GeCIP.
7. Cross-Compare subsets of CUP patients with '-omic' signatures across other tumour types thought to be overlapping significantly with CUP. About on third to one half of these patients may be variants arising from Pancreatic or pancreato-biliary origins. Both tumour types that the UK through CRUK/NCRN studies has already significant databases of clinico-translational material and either current or future genomic level data (Biankin / Grimmond for Pancreas and other NCRI funded liver surgical studies where tissue banking is funded).

**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.*

The Project governance is planned to be delivered through the network and consortium that is already involved in the CUP-ONE Trial. It will be extended to up to an additional 6-8 new representatives to achieve wider and preferably full, geographical coverage from newer CUP networks that were not in existence when CUP-ONE was running. In addition, at least 2 members should be in Palliative care (Medical /CNS / Nurse consultant or ANP), the addition of at least one user representative (John Symons from the CUP Foundation) and at least two CUP CNS/ ANP's. Critically, a minimum of 2 scientists with significant experience of genomics will be added to the Project governance team.

The structure of the proposed CUP GeCIP domain will also extend to newer networks through their clinical CUP and CNS leads that have formed more recently, that were not previously involved in the CUP-ONE network. This includes inviting the clinical CUP leads in the 144 CUP teams that were peer reviewed in 2013/14 with England-wide geographical coverage. Each team that feels they can contribute, in addition to the already established CUP-ONE Teams, will have to demonstrate the ability to have the support and infrastructure to obtain biopsies and clinical information to link in to their nominated GMC's and ECMC's to encourage specific scientific questions and proposals to the consortium. A recent unique International conference hosted in the UK (http://www.cupfoundjo.org/conference (slides available)) on the 24 September 2015, where the CUP GeCIP was discussed with participants has generated significant enthusiasm and national buy-in to supporting this as a high priority.

<u>Training and education</u>

There are substantial opportunities for this domain at all levels, especially patient- focussed care and attitudes, as well as challenges in genomic analysis, multi-omics interpretation and linkage with clinical data.

<u>Patient and Participant Involvement</u>

The CUP foundation user representative (John Symons or a nominated delegate) will be on the governance and steering committee for the CUP GeCIP. Patents who sign up to the project have historically had very poor prognoses and it has been difficult to get general patient participants and volunteers. However, they can provide feedback on the process and can be offered (as in

CUP-ONE) any outcomes to be fed back to them or their relatives. Relatives have also previously volunteered to help and have linked up with The CUP foundation and CRUK.

International collaborators

Professor David Bowtell, and Penny Schofield, are already collaborators on the CUP-ONE trial and are PI's for the Australian CUP genome sequencing project (of which H Wasan is a co-applicant) (APP1048193 Solving Unknown Primary cancER – SUPER 2013 to 2016 $599,831.00 Funding from Cancer Australia)

They are based at The Peter McCallum Cancer Institute, St Andrews Place, East Melbourne, Victoria 3002, Australia

There is a possibility of collaboration with the Sarah Cannon institute in the USA (Professor Tony Greco), but there may be IP issues to resolve before this is agreed.

Professor Nick Pavlidis is chair of the CUP group at ESMO (European society of Medical Oncology) and has indicated the interest of a joint programme of fellowships and trainees.

Industry interaction

The "Precision medicine Forum" (It has representatives from genomic enterprises, industry and academics) have engaged with the UK CUP group and discussions are already underway as to how genomic level data may help CUP patients achieve novel treatments. The next meeting is the 24th November 2015. The PMF group is led by 1) Hakim Yadi, CEO of the Northern Health Science Alliance, working to mobilise the tertiary hospitals and universities of the North for broader health impact through research, especially big data. Previously he was COO to the UKTI's Life Science Investment Organisation and with PA Consulting working across translational from university to pharma. 2) Piers Mahon is Director, Global Alliances with Cancer Commons, a US charity focusing on using big data for patient benefit. Previously, he was with Bain & Company for 14 years in their health care practice, working on stratified drug launches and 3) Irina Haivas, Principal, GHO Investment Partners. Investment manager in healthcare growth equity investing in product & technology businesses, or B2B services. Previously manager with Bain & Company specialising in pharma, biotech, and consumer health globally.

The London Cancer Alliance (LCA) has started a series of meetings with pharma to formally engage their participation with a discussion around CUP patient treatment options with the newer targeted and immunotherapy agents. A proposal to BMS has begun the engagement.

## Detailed research plan – Cancer Main Programme Gear 2 studies

| Full proposal (total max 1500 words per Gear 2 Substudy) | |
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| **Title**<br>*(max 150 characters)* | **CP01: Development of a combined genomic diagnostic expression classifier and mutational genomic signature for CUP** |
| Cohort details and scientific case | |
| Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics) | All patients at Diagnosis of confirmed CUP discussed at a specialist CUP MDT, where it is possible to get a pre-treatment core tissue sample for morphological diagnosis. By definition all patients are Stage IV. (ICD-10 codes C77-80) |
| Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)<br><br>*It is assumed that in addition there will be one germline sample per patient.* | Minimum single tissue sample from each cancer and paired blood |
| # cores per tumour (if multi-region biopsying proposed) | Minimum of two |
| Follow-up samples following first ascertainment | None |
| Purpose of analysis WGS and clinical data from this cohort of patients (brief) | The overall aim is to define the somatic molecular changes in CUP at their highest current feasible level. There is a unique opportunity in CUP (unlike any other tumour type) to combine and extend the diagnostic expression RNASeq based classification outputs that will arise from the UK CUP-ONE Trial data (expected in early 2017) to inform this GeCIP sub-study, so that tissue samples may provide coupled information on both tissue of origin and mutations (through RNA expression classifiers and somatic genetics). Furthermore the project can assess whether this is combination is also assessable in liquid biopsies (separate linked sub-study). |
| Scientific case and insights that will be gained from this cohort (more details, as indicated) | This combination of RNASeq based classification, mutation profiling and mutational signature analysis is a novel approach to genome based classifiers for cancers. If developed in CUP – it is likely that it could apply to all poorly differentiated / undifferentiated cancers irrespective of tissue of origin. This allows an opportunity to assess and catalogue expression diagnostic classifiers, which may be faster and more consistent to achieve than current manual pathological techniques with immunohistochemistry. A combined genomic approach to ascertaining the molecular diagnostic and cancer landscape of the tumour may well be quicker, easier and cheaper than a standard current complex diagnostic work-up, including multiple imaging modalities "in search of" the (elusive) primary. This analysis could also be applied across other tumour types with poor prognostic, highly metastatic phenotypes in other tumour types within The GEL programme. |

| Alignment to clinical trials | |
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| 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).<br>Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility? | There is currently no prospective CUP trials running in the UK but 1 proposal is being submitted for funding this year as a multi-centre trial of a PDL1 inhibitor in CUP. This is with a commercial organisation (Merck / Pembrolizumab) but the final costings and trial approval are pending by Q3 2017. |
| Is this sub-study a new therapeutic trial? | No. |

| Full proposal (total max 1500 words per Gear 2 Substudy) | |
|---|---|
| **Title**<br>*(max 150 characters)* | **CP02: Is it feasible to obtain genomic diagnostic expression classifier and mutational genomic signature for CUP with liquid biopsies.** |
| Cohort details and scientific case | |
| Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics) | This proposal is linked to Sub-study one i.e. identical criteria but is to correlate in a pilot whether the same information can be obtained from paired liquid biopsies at diagnosis.<br>All patients at Diagnosis of confirmed CUP discussed at a specialist CUP MDT, where it is possible to get a pre-treatment core tissue sample for morphological diagnosis. By definition all patients are Stage IV. (ICD-10 codes C77-80) |
| Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)<br><br>*It is assumed that in addition there will be one germline sample per patient.* | Minimum single tissue sample from each cancer and paired blood |
| # cores per tumour (if multi-region biopsying proposed) | Minimum of two core biopsies with baseline ctDNA |
| Follow-up samples following first ascertainment | None |
| Purpose of analysis WGS and clinical data from this cohort of patients (brief) | This proposal is linked to Sub-study one but is to correlate in a pilot whether the same or similar information can be obtained from paired liquid biopsies at diagnosis.<br><br>The overall aim is to define the somatic molecular changes in CUP at their highest current feasible level. There is a unique opportunity in CUP (unlike any other tumour type) to combine and extend the diagnostic expression RNASeq based classification outputs that will arise from the UK CUP-ONE Trial data (expected in early 2017) to inform this GeCIP sub-study, so that tissue samples may provide coupled information on both tissue of origin and mutations (through |

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| | RNA expression classifiers and somatic genetics). Furthermore the project can assess whether this is combination is also assessable in liquid biopsies (separate linked sub-study). |
| Scientific case and insights that will be gained from this cohort (more details, as indicated) | This proposal is linked to Sub-study one but is to correlate in a pilot whether the same or similar information can be obtained from paired liquid biopsies at diagnosis.<br><br>This combination of RNASeq based classification, mutation profiling and mutational signature analysis is a novel approach to genome based classifiers for cancers. If developed in CUP – it is likely that it could apply to all poorly differentiated / undifferentiated cancers irrespective of tissue of origin. This allows an opportunity to assess and catalogue expression diagnostic classifiers, which may be faster and more consistent to achieve than current manual pathological techniques with immunohistochemistry. A combined genomic approach to ascertaining the molecular diagnostic and cancer landscape of the tumour may well be quicker, easier and cheaper than a standard current complex diagnostic work-up, including multiple imaging modalities "in search of" the (elusive) primary. This analysis could also be applied across other tumour types with poor prognostic, highly metastatic phenotypes in other tumour types within The GEL programme. |
| 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).<br>Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility? | There is currently no prospective CUP trials running in the UK but 1 proposal is being submitted for funding this year as a multi-centre trial of a PDL1 inhibitor in CUP. This is with a commercial organisation (Merck / Pembrolizumab) but the final costings and trial approval are pending by Q3 2017. |
| Is this sub-study a new therapeutic trial? | No. |

| Full proposal (total max 1500 words per Gear 2 Substudy) | |
|---|---|
| **Title**<br>*(max 150 characters)* | **CP03: Comparing the combined genomic diagnostic expression classifier and mutational genomic signature for CUP, in tumours defined as GI or lung across the relevant respective GeCIP domains (CRC, Upper GI and lung)** |
| Cohort details and scientific case | |
| Cohort eligibility definition (disease type, sub-type, presentation, stage, treatment, clinical characteristics, epidemiological characteristics) | This proposal is linked to Sub-study one i.e. identical criteria but is to correlate, compare and contrast the data outputs obtained from sub-study one, with the common expected expression classifiers of tissue of origin obtained in other |

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| | GeCIP domains that are expected to arise from current CUP studies.<br><br>All patients at Diagnosis of confirmed CUP discussed at a specialist CUP MDT, where it is possible to get a pre-treatment core tissue sample for morphological diagnosis. By definition all patients are Stage IV. (ICD-10 codes C77-80) |
| Samples per patient at first ascertainment (primary tumour, LNs, metastatic sites)<br><br>*It is assumed that in addition there will be one germline sample per patient.* | minimum single tissue sample (from sub-study one) from each cancer and base-line paired blood |
| # cores per tumour (if multi-region biopsying proposed) | Minimum of two core biopsies |
| Follow-up samples following first ascertainment | None |
| Purpose of analysis WGS and clinical data from this cohort of patients (brief) | This proposal is linked to Sub-study one but is to correlate the data across GeCIP domains when the tissue classifier purports a site of origin of the primary (currently 3 classifiers being compared in CUP-ONE)<br><br>There is a unique opportunity in CUP (unlike any other tumour type) to combine and extend the diagnostic expression RNASeq based classification outputs that will arise from the UK CUP-ONE Trial data (expected in early 2017) to inform this GeCIP sub-study, so that tissue samples may provide coupled information on both tissue of origin and mutations. (through RNA expression classifiers and somatic genetics). |
| Scientific case and insights that will be gained from this cohort (more details, as indicated) | This proposal is linked to Sub-study one but is to correlate to other GeCIP domains, when the tissue based classifier points to a purported site of origin. Currently the data from expression classifiers are suggesting that the tissue of origin from CUP by the newer RNA expression technologies are arising from a GI source (Pancreato-biliary (30-50%) ; CRC & small bowel 10-15%; and lung (10-20%). There are also smaller percentages of renal, breast and others. This proposal would thus compare the mutational genomic profiles generated by the Other GeCIP's (particularly the highly metastatic phenotypes) that overlap with the diagnostic information generated from the CUP tissue-based expression classifier that suggest a site of origin is GI or lung.<br><br>This is an opportunity to assess and catalogue expression diagnostic classifiers in CUP and assess whether the genomic mutational patterns are similar across other tumour types where a site of origin is purported in highly |

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| | metastatic or poorly differentiated disease. |
| 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).<br>Is co-recruitment to this trial/study optional/mandatory for recruitment to this cohort eligibility? | There is currently no prospective CUP trials running in the UK but 1 proposal is being submitted for funding this year as a multi-centre trial of a PDL1 inhibitor in CUP. This is with a commercial organisation (Merck / Pembrolizumab) but the final costings and trial approval are pending by Q3 2017. |
| Is this sub-study a new therapeutic trial? | No. |

| Data and informatics requirements |
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| 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 | |
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| **GeCIP domain name** | Cancer of Unknown Primary |
| **Project title** *(max 150 characters)* | **Cancer of unknown primary 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.