Domain application form: **Stratified Healthcare and Therapeutic Innovation Genomics England Clinical Interpretation Partnership**

1. PEOPLE

Role	Experience
Domain lead m.j.caulfield@qmul.ac.uk **Sub-domain leads:** m.r.barnes@qmul.ac.uk m.seymour@ncrn.org.uk patrick.chinnery@mrc-mbu.cam.ac.uk munirp@liverpool.ac.uk	**Domain Lead: Professor Mark Caulfield** FMed Sci is Chief Scientist for the 100,000 Genomes Project and a Clinical Pharmacologist with a cardiovascular gene discovery programme with the aim of therapeutic innovation. He is an NIHR Senior Investigator and has been amongst the World's Most Highly Cited researchers since 2014. **Target Discovery: Sub-Domain Lead - Dr Mike Barnes** is Director of Bioinformatics at Queen Mary University of London and specialises in druggability assessment for gene discoveries. He is a major contributor to multiple MRC Stratified Medicine Consortia where he provides analytical support. **Innovative Clinical Trials: Sub-Domain leads – Cancer Trials are led by Prof Matt Seymour**, Clinical Research Director of the National Cancer Research Institute and Director of the NIHR Clinical Research Network in Cancer. He is also a member of the Genomics England Science Advisory Committee. **Rare Disease Trials are led by Prof Patrick Chinnery** FMed Sci is at the MRC Mitochondrial Biology Unit at Cambridge and co-leads the NIHR BioResource and the Translational Research Collaborative in Rare disease geared to attract new trials to the UK. **Pharmacogenomics: Sub-Domain Lead - Professor Sir Munir Pirmohamed** is David Weatherall Chair in Medicine at the University of Liverpool, and holds the NHS Chair of Pharmacogenetics in the UK, and is Deputy Director of the M.R.C. Centre for Drug Safety Sciences, and Director of the Wolfson Centre for Personalised Medicine. He is NIHR Senior Investigator, Fellow of the Academy of Medical Sciences in the UK. He has authored over 300 peer-reviewed publications focused on individual variability in drug response, both safety and efficacy, and identifying strategies to personalise medicines in order to optimise drug efficacy and minimise toxicity.
Domain deputies	**Subdomain 1: Target Discovery: Bissan Al Lakzani and Chas Bountra.** **Sub-domain 2: Innovative Clinical Trials: Prof Max Parmar.** **Subdomain 3: Pharmacogenomics: Dr Ana Alfirevic's** research focuses on molecular pharmacology and pharmacogenetics and adverse drug reactions including drug-induced hypersensitivity, hepatotoxicity, antipsychotic drug-induced agranulocytosis and statin-induced myotoxicity.
GMC representative Dr Angela Douglas	Angela Douglas, a Consultant Clinical Scientist, in the Genetics Laboratory Service at Liverpool Women's Hospital, and is working with NHSE on the 100,000 Genomes Project.
Patient representative Mrs Jane Shear	Jane Shear is an active member of the Patient Public Involvement Group at the University of Liverpool. She is involved in the research of Pharmacogenetics and drug safety, particularly interested in and contributing to the Stevens Jonson syndrome (SJS) awareness group that supports those affected by some of the most severe forms of adverse drug reactions.
Education and Training lead Dr Lynn Greenhalgh	Lynn Greenhalgh is Consultant Clinical Geneticist at the Liverpool Women's Hospital special clinical interest is primarily cancer genetics, where she takes a lead for cancer genetics across Cheshire and Merseyside and is leading the North West Coast Genomics Healthcare Educational Group.
Validation and Feedback representative Professor William Newman **Electronic Health GeCIP representative** Prof Harry Hemingway	Prof Newman is a Professor of Translational Genomic Medicine at the University of Manchester with special interest in rare disease discovery and cancer. His expertise is in Pharmacogenomics and a lead for the Validation and Feedback GeCIP. Prof Hemingway is Director of the current Farr London Node and is lead of the Electronic Health GeCIP domain

Other domain members

Name	Affiliation	Position	Area of interest	Contribution
Bissan Al Lakzani	Institute of Cancer Research	Professor	Target Discovery	The canSAR software
Chas Bountra	Oxford	Professor	Structural Biology and Target discovery	The Structural Genomics Consortium
Max Parmar	University College London	Professor	Trial Design	Adaptive Trials Design
Bobby Gaspar	University College London	Professor	Gene Therapy	Gene editing
Harry Hemingway	University College London	Professor	Electronic Health	Electronic Health
Ana Alfirevic Deputy of the Pharmacogenetics Sub-domain	University of Liverpool	Senior Lecturer in Pharmacogenetics	Pharmacogenomics Molecular pharmacology	Coordination, molecular genetics and diagnostics, interpretation
Ann Daly	University of Newcastle	Professor of Pharmacogenetics	Pharmacogenetics, Molecular Pharmacology	Molecular genetics and pharmacogenetics
Ewan Pearson	University of Dundee	Professor of Diabetic Medicine	Pharmacogenetics, Stratified medicine, Drug efficacy, Drug outcomes, Diabetes	Clinical pharmacology and pharmacogenetics of complex diseases
Andrew Morris	University of Liverpool	Professor in Statistical Genetics	Genomic Epidemiology	Statistical Genetics, Epidemiology
Andrea Jorgensen	University of Liverpool	Lecturer in Biostatistics	Pharmacogenetics, Methodological Quality, Systematic Reviews and Meta-Analysis	Statistical Genetics
Colin Palmer	University of Dundee	Professor of Pharmacogenetics	Pharmacogenomics, GWAS, NGS	Pharmacogenomics
Richard Ashcroft	Queen Mary University of London,	Professor of Bioethics, Co-Director Centre for the Study of Incentives in Health Bioethics	ethical challenges in public health	Medical Law and ethics
Christine McNamee	University of Liverpool	UK Pharmacogenetics and Stratified Medicine Network Manager	Developing multidisciplinary collaborative partnerships	Communication, networking, Disseminating information to the wider scientific community
William Newman	University of Manchester	Professor of Translational Genomic Medicine	Rare disease gene discovery and cancer	Clinical genetics
Dyfrig Hughes	University of Bangor	Professor of Pharmacoeconomics	Pharmaceutical economics	Health Economics

Krishna Prasad	MHRA	Clinical Assessor	Clinical Pharmacology	Regulatory issues
Carla Deakin	NICE	Associate Director – Diagnostics Assessment Programme	Evaluation of clinical and cost-effectiveness of diagnostics leading to the production of NICE Diagnostics Guidance Documents for use within the NHS	NICE Guidelines
Dan Hawcutt	University of Liverpool	Senior Lecturer Paediatric Clinical Pharmacology	Paediatric pharmacogenomics	Paediatric pharmacogenomics
Ellen McDonagh	Queen Mary University of London	Lead Scientific Curator, Genomics England	Curation and knowledgebase	Genetic variant annotation and interpretation, knowledge curation, meeting and network coordination
Nick Watkins	NHS Blood and Transplant	Assistant Director – Research and Development	Genomics, Translational research, Strategy	Strategy and delivery
Jane Shear	N/A	Patient representative	Serious cutaneous adverse drug reactions	Patient public engagement via SJS Awareness Group
Angela Douglas	Liverpool Women's Hospital	Consultant Clinical Cytogeneticist	Cytogenetics	Cytogenetics and complex chromosomal variants
Lynn Greenhalgh	Liverpool Women's Hospital	Consultant Clinical Genetics	Clinical Genetics	North West Coast Genomics Healthcare Educational Group lead

The proposed team comprises the multi-disciplinary team of UK experts Target Discovery, Innovative Clinical Trials and Pharmacogenomics connected to all the relevant National Institute for Health and MRC infrastructure and supported by the UK Pharmacogenetics and Stratified Medicine Network (PSMN) chaired by Pirmohamed. We include expertise that covers all age groups from children to adults, and would thus be consistent with the age groups being targeted by the 100K genomes project.

The team has many individuals who have long-standing experience in training, and in implementation of new technology through the development and validation of new diagnostics.

The team comprises clinicians, scientists, health economics experts, ethicists, educationalists, statistical geneticists, drug regulators and policy makers.

The group thus has excellent expertise to address Target Discovery, Innovative Trials and Pharmacogenomics in terms of discovery, interpretation and implementation of knowledge and has links throughout the world in order to initiate global research collaborations.

Potential international collaborators	Through the many organisations we are involved with worldwide, we will be able to collaborate with a number of partners where appropriate. The organisations/networks which will serve as potential collaborators (and members therein) include: • Open PHACTs (an international not for profit organisation) • NIHR Clinical Research Network in Genetics, Cancer and Organ based Specialty Groups • The NIHR BioResource and the Translational Research Collaborative in rare disease • NIH Pharmacogenomics Research Network • European Society of Pharmacogenomics and Personalised Therapy • EU Pharmacogenomics Research Network • IUPHAR pharmacogenomics section • SE Asian and the South Korean Pharmacogenomics Research Network • Clinical Pharmacogenetics Implementation Consortium (CPIC) • Pharmacogenomics Knowledge Base (PharmGKB) • European Medicines Agency (EMA) Pharmacogenomics Working Party • PiCA Consortium - Pharmacogenomics in Childhood Asthma We have specific contacts and/or hold advisory positions in each of these networks which can be used to form collaborations.

2. DOMAIN DETAILS

Domain Name	Cross-cutting: **Stratified Healthcare and Therapeutic Innovation Genomics England Clinical Interpretation Partnership**
Introduction	The development of a new medicine costs approximately $2-3bn and is increasing which reflects both the true cost of successful development, but also late stage attrition where perhaps 80% of medicines fail. The Genomic Medicine era offers substantial potential to prime therapeutic innovation (small molecule, biologic or gene targeted therapies), offer adaptive trials stratified by multi-omics profiling and use real world pharmacogenetics data to select the optimal medicine first time and identify risks of genomically driven side effects. This GeCIP domain proposal is designed to harness the strength of UK infrastructure, such as the NIHR Clinical Research Network, the Stratified Medicine Network and the Structural Genomics Consortium. The formation of a stratified healthcare and therapeutic innovation domain within the Genomics England Clinical Interpretation Partnership will provide the platform for a major scientific and healthcare initiative in this area. It will capitalise upon existing strengths and infrastructure and develop new partnerships to maximise patient benefit and industry partnership.
Sub domains	**Sub domain 1: Target Discovery – Mike Barnes (Queen Mary), Bissan Al Lakzani (Institute of Cancer Research).** This GeCIP sub-domain will use available suites of software to evaluate the druggable genome for rare disease and cancer discoveries made by the 100,000 Genomes Project. The approach taken by this sub-domain will be to take advantage of major initiatives with extant industry interest such as the Open PHACTS suite of software and the Structural Genomics Consortium as any development will require their involvement. More generally, the subdomain will identify genes that are observed to have biallelic loss of function (LOF) in healthy individuals for target development. **Open PHACTS (Mike Barnes):** A recent approach to address these issues is the integration of data from multiple different sources by means of semantic web technologies has led to the Open Pharmacological Concepts Triple Store (Open PHACTS) is an Innovative Medicines Initiative Knowledge Management project (IMI - 2nd call 2009). The Open PHACTS Discovery Platform offers a software suite include ChEBI, ChEMBL, SureChEMBL, ChemSpider, ConceptWiki, DisGeNET, DrugBank, Gene Ontology, neXtProt, UniProt and WikiPathways. By drawing together multiple sources of publicly-available biomolecular, pharmacological and physicochemical data, Open PHACTS

	and reproducible way. This was created from an Innovative Medicines Initiative so has significant industrial buy in so could provide a within Genomics England package to prime genomic therapeutic discovery. **The CanSAR software suite** (http://cansar.icr.ac.uk) created by **Bissan Al Lakzani** is a publicly available, multidisciplinary, cancer-focused knowledgebase which integrates genomic, protein, pharmacological, drug and chemical data with structural biology, protein networks and druggability data. It is used by 150,000 people worldwide to rapidly access information and help interpret experimental data in a translational and drug discovery context. canSAR's aim is to provide comprehensive multidisciplinary annotation for genes and biological systems to enable target validation and drug discovery in canSAR. http://cansar.icr.ac.uk/cansar/data-sources/). **The Structural Genomics Consortium – Prof Chas Bountra (Oxford).** This initiative is funded by AbbVie, Bayer, Boehringer Ingelheim, Genome Canada through Ontario Genomics Institute Grant, GlaxoSmithKline, Janssen, Lilly Canada, Merck, Novartis Research Foundation, the Ontario Government, Pfizer, Takeda, and Wellcome Trust funding. This is a large-scale pre-competitive consortium that catalyses research in new areas drug discovery focusing explicitly on less well-studied areas of the human genome. They have major programmes in DNA methylation, structural biology, target characterisation and recombinant antibodies. They have deposited more than 1500 high-resolution structures of medically relevant human proteins in public databases and generated 100's of recombinant antibodies with therapeutic potential. **Sub domain 2. Innovative Clinical Trials – Leads: Matt Seymour (Leeds) & Patrick Chinnery (Cambridge).** The UK translational environment has an extremely strong platform due to NIHR, Higher Education and NHS investment in state of the art infrastructure for clinical research. The 100,000 Genomes Projects wishes to harness the potential opportunities from the National Institute for Health Research Infrastructure. The NIHR Clinical Research Network metrics show increasing trials UK-wide, greater industry studies and enhanced performance to time and target. More than 665,000 participants took part in clinical research studies supported by the Network in 2016-17. This is 10 per cent more than the previous year. Nearly 35,000 participants were recruited to studies sponsored by the life sciences industry. This has meant that over the last five years, more than 150,000 participants have had the opportunity to participate in high quality life sciences industry research and access cutting edge treatments. The new Health Data Research Institute offers potential to use the electronic health records of participants to follow-up participants in early phase trials over their life course or to do innovative trials in rare disease using real world data (this connects with the Electronic Health GeCIP). **Cancer Trials – Lead: Prof Matt Seymour (Leeds).** The National Cancer Research Network and Institute represent a powerful framework for attracting new cancer trials alongside whole genome sequencing. The National Cancer Research Network has over 1000 clinical trials operating throughout the UK alongside which a re-engineered molecular and digital pathology in the NHS could attract significant new opportunities to the UK. This could sit extremely well with non-exclusive partnerships with Clinical Research Organisations, such as Quintiles IMS, who might take the offering of application of whole genome sequencing into bid defence to attract new clinical trials in cancer and rare disease into the UK. **Rare Disease Trials and the NIHR Translational Research Collaborative – Lead: Prof Patrick Chinnery (Cambridge).** This will harness opportunities from the above NIHR investments to attract new trials in rare disease to the UK using the framework of the 100,000 Genomes Project. It will be possible from the new NHS Commissioned service to identify patients across the full repertoire of diseases using Many exciting new therapies are becoming available, and efficient designs to identify effective treatment regimens in a timely fashion are essential. In rare disease the excitement of gene editing of the somatic genome, renewed endeavour in gene therapies and potential in rare disorders fir cell-based therapy means we wish to specifically include Prof Bobby Gaspar and Prof Robin Ali in this sub-domain. **Innovative Clinical Trial Design: Lead: Prof Max Parmar (UCL)**.leads the MRC Clinical Trials Unit at UCL has pioneered efficient adaptive designs such as multi-arm, multi-stage (MAMS) design. In the multi-arm element, several regimens are simultaneously assessed against a common control group, within a single randomised trial. In the multi-stage element, patient recruitment is discontinued to research arms that are not showing sufficient efficacy, based on a series of pre-planned, interim, lack-of-benefit analyses. One advantage the MAMS design has over other types of adaptive design

	is that it utilises an 'intermediate' outcome measure at the interim stages. This makes the design more efficient, because the expected number of patients and the length of time taken to complete the trial will be dramatically reduced. It also allows researchers to design a MAMS trial as a seamless phase II/III trial, further streamlining the treatment evaluation process. **The Health Data Research UK Institute and Real World Clinical Trials – Lead: Harry Hemingway (UCL).** The new Health Data Research UK Institute is currently receiving regional applications to create a new MRC Centre (previously known as the Farr Institute) which provides the opportunity to undertake state of the art electronic health research. There is an extant Electronic Health Record GeCIP domain and an increasing opportunity for such an infrastructure to undertake real world trials where people are monitored via remote devices or in general practice with electronic health data recovery. Even though the randomised controlled trial remains the gold standard for medicines development but industry are beginning to question the applicability to the broader population and models such as the Glaxo Smith Kline Salford Lung Study recruited and entirely run in Primary Care may become an important model for affordable later phase trials. **Sub domain 3. Pharmacogenomics: Lead Prof Sir Munir Pirmohamed (Liverpool).** This aims to: 1) increase pharmacogenomics knowledge by identifying novel rare variants in pharmacogenes and drug targets that may contribute to drug response, and investigate/validate their function; 2) provide interpretation of results to guide and develop implementation of pharmacogenomics into clinical practice in support of the NHS Pharmacogenomics Working Group; and 3) assess the ethical issues of identifying pharmacogenetic variants in individuals who may need drug treatments that show variation in response. In partnership with several other GeCIP cross-cutting domains and in collaboration with international leaders in pharmacogenomics research, we will set scientific priorities and train healthcare professionals, patients and the public to reach the goal of better medicines and stratified/personalised healthcare globally. The domain will include a multidisciplinary team with clinical, academic, ethics, regulatory, and health economics expertise.
Research and discovery	The objectives of the Stratified Healthcare and Therapeutic Innovation GeCIP are to: **1) Increase Target discovery, Innovative Clinical Trials and pharmacogenomics knowledge** • Use Open Phacts, canSAR and the Structural Genomics Consortium to generate new targets and validate them • Study genes with biallelic LOF in healthy individuals to generate new targets and validate them • Generate novel trials in cancer and rare disease and harness the recall for patients to studies in the UK. • Create novel gene therapy, gene editing and cell therapy trials using the framework of the 100,000 Genomes Project and successor NHS commissioning. • Increase knowledge of and confirm the presence and role of pharmacogenomics variants, complex structural variants and haplotypes in pharmacogenes including identification of novel rare variants that may contribute to drug response contributing meta-analyses where possible. • Compare common/rare somatic and germline genetic variants in pharmacogenes and known drug targets in data from cancer patients. **2) Conduct, analyse and interpret the results of the Target Discovery, Innovative Trials and the pharmacogenomics sub-domains and translate these into clinical practice** • Together with international collaborators, provide guidelines to implementation of into clinical practice. Utilise bioinformatic analytical methods to develop clinical decision support software. • Knowledge exchange with SMEs to develop simple low cost pharmacogenetic tests suitable for clinical practice in non-specialist laboratories. **3) Assess the ethical issues related to these findings** • Explore the ethical issues related to incidental findings on drug response and develop protocols/materials for aiding the explanation of these issues to patients and health care professionals. • Provide education and training on Target Discovery, Innovative Trials and Pharmacogenomics to health care professionals, public and patients.

	identified above will require close inter-disciplinary working, for example with bioinformaticians from Genomics England and others.
Legacy series for sequencing	We are aware of several studies currently being undertaken in Europe and the US that utilise whole genome and whole exome sequencing approaches. We will have access to the sequencing data, which will together with the information from the 100,000 genomes project will allow us to collaborate internationally and with industry on Target Discovery, Clinical Trials and Pharmacogenetics across different ethnicities. In addition to NGS data, by generating additional transcriptomic, epigenetic, proteomic, metabolomic, lipidomic and other –omics data that will be available for bioinformatic analyses we will be able to evaluate the clinical added value of these data for the NHS.
Current Funding	• UK Clinical Genomics Infrastructure - £24 million –research platform for the 100,000 Genomes Project • NIHR Biomedical Research Centres at UCLH, Barts, Cambridge (NIHR BioResource) and the Royal Marsden 2017-2022 • MRC Mitochodrial Biology Unit at Cambridge and the MRC Clinical Trials Unit at UCL • NIHR Clinical Research Network in Cancer, Genetics and other Organ based specialities • MRC Centre for Drug Safety Sciences. MRC Renewed from 1 April 2014 £2.7 million (Director). • North West England MRC Fellowships in Clinical Pharmacology and Therapeutics. MRC (and Industry partners including GSK, AZ, ICON); £3,012,100 (£1,598,751 from MRC). 2010-2016 (Programme Leader). • The interactions between Clostridium difficile, intestinal microbiota and the host response in hospitalised patients. MRC Program Grant; £2,400,000; 2012-2017 (co-applicant, 4 co-investigators). • Applying innovative technologies to improve the benefit-risk ratio of drugs: developing a national resource underpinned by the infrastructure of the MRC Centre for Drug Safety Science. Medical Research Council Clinical Research Infrastructure Award.; £5,000,000 (Principal applicant, 4 co-investigators). • 2015-2020, £1 mil, Harris Foundation, Wellbeing of Women, Harris Centre for Preterm Birth, • 2012-2017 £2.35 mil. IMI, MIP-DILI (Euro 37mil) Improving the early prediction of drug induced liver injury in man
Plans for further funding	Potential funding sources that will be utilised for further researcher here will include the MRC, NIHR, Wellcome Trust, possibly H2020 and industry. Depending on the scope and nature of funding available the individual sub-domains will apply for an overall programme of work or individual areas. This will be done collaboratively within each sub-domain.
Patient representation	**Rare Disease and Cancer representation** • We are seeking representation to steer and engage in the Target Discovery and Innovative Trials sub-domains. **Pharmacogenetics:** • Raising Awareness of Stevens-Johnson Syndrome (SJS) - SJS and its more severe form toxic epidermal necrolysis (TEN) are serious diseases caused by medications. Clinical symptoms include skin blistering accompanied by mucous membrane ulceration and eye involvement that can lead to blindness. On the 3rd February, Professor Pirmohamed and members of his team attended the Houses of Parliament in support of the 'SJS Awareness Campaign'. The campaign, developed and driven by patients and carers affected by SJS, was launched by the Rt Hon Margaret Hodge MP and provided the opportunity for patients and carers to share their stories. Margaret Hodge in her address at the event

	vowed to give her full support to raising awareness of this debilitating disease. • An awareness poster designed by the patients group and the staff at the Wolfson Centre for Personalised Medicine will be disseminated and displayed in NHS Trusts and GP practices across the country with the aim to educate health professionals and general public. • We are currently conducting a systematic review of randomised controlled trials on pharmacogenetics of drug induced skin rash within the Cochrane Skin Group based in Nottingham. The protocol for the review has been published in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016870). Patient representatives are active.
Education and Training	**All sub-domains** Education and training of clinicians, scientists, and healthcare professionals will be provided through several successful education schemes, which will complement the existing GeCIP cross-cutting domains, including the Validation and Feedback, Analytical and Ethics and Education Domains. These will be within the existing teaching programmes which are being developed as part of the NHS Health Education England MSc Genomic Medicine initiatives and their genomics education programme, but also outwith within potential teaching programmes in the Universities of individual members. **Specific initiatives in Pharmacogenetics** Engagement of patients and the general public will be structured through the UK Pharmacogenetics and Stratified Medicine Network (Lead: Pirmohamed), the European Pharmacogenomics Research and Implementation Network (Lead: Alfirevic), the North West Pharmacogenomics research Group (Alfirevic, Newman), the British Pharmacological Society (BPS Ambassador Hawcutt) and through the Patient Public Involvement groups (SJS awareness group, CLAHRC PPI). The PSMN holds focused workshops to develop a consensus of opinion on key topics within stratified medicine. We will also be able to leverage further engagement, when necessary and appropriate, by liaising with individual programmes in the Universities and NHS Trusts of members in this GeCIP.
Mechanisms for Pre-competitive Interaction with Industry	**Selected Industry partners for potential partnership:** Direct engagement with SMEs and large pharma/biotech where partnership will likely not be precompetitive. Quintiles IMS – clinical trial generation partnership Thermofisher- Prospective evaluation of point-of-care (POC) procalcitonin testing in infective exacerbations of chronic disease in childhood, to improve care and reduce health inequalities MC Diagnostics- Development of HLA genotyping panel to predict serious immune mediated adverse drug reactions