GeCIP Detailed Research Plan Form

September 2018

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	**Health Economics**
Project title *(max 150 characters)*	Applying and further developing health economic methods to better understand the economic impact of Whole Genome Sequencing (WGS) in clinical practice and the incentives for economic evidence generation

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

The objectives of our research are to:

1. Produce guidance on the most appropriate use of whole genome sequencing and other sequencing technologies in routine clinical care, in terms of establishing their economic value and affordability;
2. Establish how the non-health consequences of sequencing should be valued as well as health outcomes;
3. Provide evidence of the preferences of key stakeholders for different genomic tests, and also for alternative forms of service delivery;
4. Demonstrate the opportunities and challenges of using linked genomic, clinical and health care resource use data and produce some potential solutions to key challenges;
5. Provide guidance on current and expected capacity, demand, activity and patient flow of sequencing to allow the identification and quantification of bottlenecks and their estimated impact on service delivery;
6. Facilitate training and education in the methods used to perform economic evaluation, tailored to the genomics context, for those who will be making policy decisions locally, regionally, nationally and internationally.

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)*

Genomic technologies have shown promise for stratifying disease management, identifying patients with rare disorders and identifying the causes of infections, all of which could improve both health and non-health outcomes for patients. The 100,000 Genomes Project (100KGP) presents an ideal opportunity to systematically collect high-quality cost and health outcome data within the largest genome sequencing programme in the UK, in an NHS setting. This data, when used in the context of economic evaluations, will be able to provide information on where the use of whole genome sequencing (WGS) is most likely to represent value for money for the NHS. This analysis will include the examination of both appropriate diagnostic points in the care pathway and also the downstream consequences of testing (such as the use of targeted drug therapies). The 100KGP also provides a fantastic opportunity to address a range of methodological challenges facing health economists in this area.

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)*

The 100KGP presents an ideal opportunity to systematically collect high-quality cost and health outcome data within the largest genome sequencing programme in the UK, in an NHS setting. We will use data from the 100KGP to evaluate the benefits and costs of using WGS to diagnose disease and we will use interviews and surveys with patients and families to find out about their

diagnostic journey and their views about whole genome sequencing.

This data, when used in the context of economic evaluations, will be able to provide information on where the use of whole genome sequencing (WGS) is most likely to represent value for money for the NHS. This analysis will include the examination of both appropriate diagnostic points in the care pathway and also the downstream consequences of testing (such as the use of targeted drug therapies). 100KGP also provides a fantastic opportunity to address a range of methodological challenges facing health economists in this area.

The following key outputs are planned:

1. Guidelines for optimum economic evaluation in genomic medicine to ensure consistency and quality in economic evaluation in this area as a legacy of the 100KGP;
2. Guidance on whether non-health consequences should be valued using a welfarist or extra-welfarist approach;
3. Information on how these non-health consequences should be traded-off against health;
4. Evidence of the preferences of key stakeholders for different genomic tests, and also for alternative forms of service delivery;
5. Demonstration of methodological and policy approaches to link genomic, clinical and resource evidence generation;
6. Guidance on current and expected capacity, demand, activity and patient flow to allow the identification and quantification of bottlenecks and their estimated impact on service delivery;
7. Training and education in the methods used to perform economic evaluation, tailored to the genomics context, for those who will be making policy decisions locally, regionally, nationally and internationally.

Expected start date	Some of this work has already started
Expected end date	

Lead Applicant(s)	
Name	Dr. Sarah Wordsworth
Post	Associate Professor and University Research Lecturer
Department	Health Economics Research Centre, Nuffield Department of Population Health
Institution	University of Oxford
Current commercial links	

Administrative Support	
Name	
Email	
Telephone	

Subdomain leads		
Name	**Subdomain**	**Institution**
Prof. Katherine Payne	Outcomes	University of Manchester
Dr. James Buchanan	Stakeholder Preferences	University of Oxford
Dr. Gurdeep Sagoo	Capacity and Implementation	University of Leeds

Detailed domain research plan

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	Applying and further developing health economic methods in order to better understand the economic impact of Whole Genome Sequencing (WGS) in clinical practice and the incentives for evidence generation

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.*

Genomic technologies have shown promise for stratifying disease management, identifying patients with rare disorders and identifying the causes of infections, all of which could improve both health and non-health outcomes for patients.

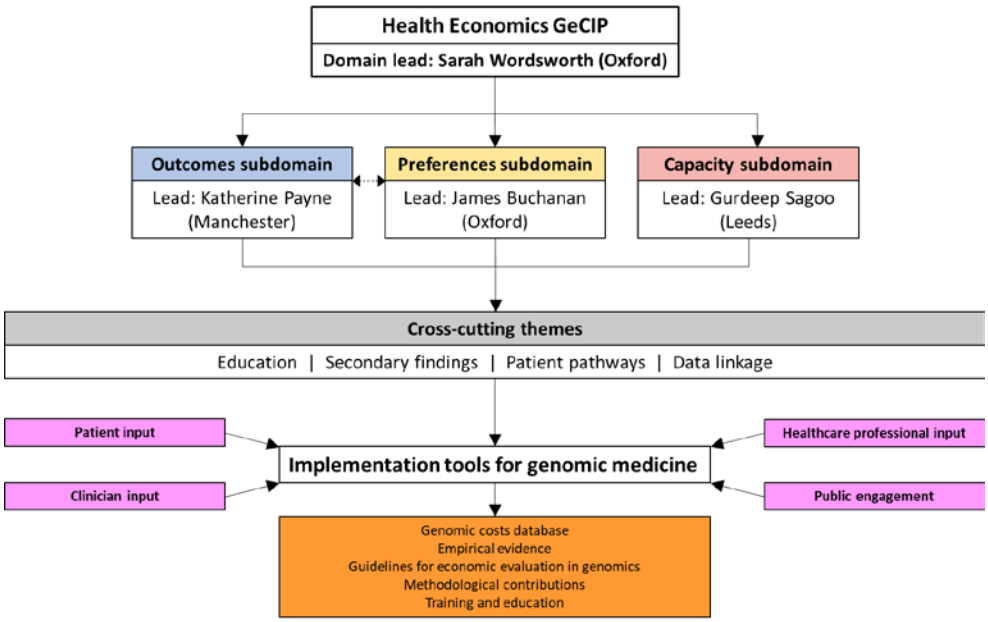
Next generation sequencing technologies have had a limited impact on patient management to date, and have not been translated on a large scale from research into clinical practice. This is in part due to a lack of high-quality translational research evidence on the clinical and health economic implications of using this genomic information. This evidence gap is a consequence of the numerous challenges that genomic testing poses for health economists, including the need to collect costs in a data-limited environment, the complex interactions between genomic mutations and health outcomes, concerns regarding the use of standard outcome measures such as quality adjusted life years (QALYs), uncertainty regarding the appropriate choice of economic evaluation approach, and limited incentives for manufacturers and payers to generate appropriate economic evidence. A further challenge is the need to identify and value the preferences of a wide range of stakeholders – including patients, service providers, and the public – when introducing new genomic technologies and formulating new models of service delivery. The work proposed in this research plan is required to tangibly address important evidence gaps in order to create a framework for objective comparisons and evaluations of costs and outcomes of genomic medicine (see below), in order to allow WGS to be implemented in the most efficient way for maximum patient benefit.

The 100,000 Genomes Project presents an ideal opportunity to systematically collect high-quality cost and health outcome data within the largest genome sequencing programme in the UK, in an NHS setting. This data, when used in the context of economic evaluations, will be able to provide information on where the use of whole genome sequencing (WGS) is most likely to represent value for money for the NHS. This analysis will include the examination of both appropriate diagnostic points in the care pathway and also the downstream consequences of testing (such as the use of targeted drug therapies). The 100KGP also provides a fantastic opportunity to address a range of methodological challenges facing health economists in this area.

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 domain has three subdomains (studying issues related to (1) outcomes, (2) preferences and (3) capacity and implementation (which includes cost-analyses) with cross-cutting themes (which will explore issues related to patient pathways, secondary findings, record linkage of health economic data and education and training). The domain's work evaluating the benefits and costs of WGS to diagnose diseases will be based on data from the 100,000 Genomes Project and draw on interviews and surveys with patients and families to find out about their diagnostic journey and their views about whole genome sequencing. Together, the different work strands will produce an assessment of the impact of having a diagnosis on patient health, quality of life and

social support.



New genomic technologies informed by the 100,000 Genomes Project are likely to take one of two forms: (i) genomic-based diagnostics for inherited rare conditions and (ii) genomic-based stratified treatment strategies. The **Outcomes** subdomain will use exemplars of new genomic-based diagnostics to (1) collate empirical data to support whether non-health benefits should be considered and paid for by the NHS; (2) understand whether non-health consequences should be valued using (i) a welfarist (WTP) or (ii) extra-welfarist (using an adapted QALY) approach; (3) determine how these non-health consequences should be traded-off against health, and (4) determine how to take account of non-health benefits in the opportunity costs. It is likely to be straightforward to value treatment strategies using a measure of health status as there are clear and measurable potential changes in health benefits that can be captured (such as improved morbidity or survival). However, new genomic-based diagnostics for rare disease, while improving the probability of patients and families gaining a diagnosis, may not offer subsequent treatment options.

In order to inform the full integration of genomic medicine into the NHS, the **Preferences** subdomain is focused on eliciting the preferences of these key stakeholders using well-established health economic approaches, primarily stated preference valuation surveys. Three stakeholder groups are particularly important: patients, clinicians and healthcare professionals. It is important to quantify the preferences of these groups for the provision and use of genetic diagnostic risk information from WGS (particularly if this does not have therapeutic consequences), and also their views on the value of stratifying treatments for diseases such as cancer. In addition, it is crucial that we fully understand how these stakeholders would like the future genomic testing service to be delivered.

Finally, the **Capacity and Implementation** subdomain will perform economic evaluations of different service delivery models. By mapping current and predicted capacity, demand, activities and patient flow, potential bottlenecks in service delivery will be identified and their estimated impact on patient outcomes quantified. This serves to elicit how genomic technologies and their outcomes will impact on demand and capacity both within clinical genetics services and in the wider NHS. This domain will also carry out two further key programmes:

The *Incentives for Evidence Generation* work stream will explore the costs associated with generating the evidence that is required to support WGS applications and consider which

reimbursement policies could provide the necessary resources. This is necessary because cost-based reimbursement for tests and inflexible pricing for companion medicines do not provide sufficient incentive for test developers or stratified medicine manufacturers to invest the resources required to develop and validate genetic tests with an appropriate evidence base. Furthermore, a narrow concept of value is employed in current NICE policies and traditional economic evaluation methods which does not reflect other potential sources of value that could be derived from genomic technologies e.g. the "value of knowing".

The *Implementation Tools for Genomic Medicine* work stream intends to provide practical tools and policy recommendations to enable policymakers to develop supportive policies and make robust decisions for the implementation of genomic medicine in the NHS.

Apart from Education & Training (see below), the work emanating from these subdomains will be relevant to issues across three cross-cutting themes.

1. Firstly, to set out an economic framework to explore where sequencing could be added to **patient care pathways** in order to maximise patient benefits. There could be a case for introducing sequencing much earlier in the patient pathway, thus avoiding the 'simpler' tests in the first place, especially if it is likely that most people will ultimately undergo sequencing regardless.
2. Secondly, there are important questions for health economists to address in terms of the costs and consequences of acting (or not acting) on **secondary findings**. One such questions is to consider whether the provision of information on secondary findings could be considered as a standard part of the patient care pathway
3. Thirdly, the domain intends to draw in **data linkage**, performing a pilot test on a sample of patients across several disease areas and attempt to link data across different databases to evaluate whether WGS improves patient outcomes (and at what cost), and to highlight potential issues arising from the linkage of genomic and clinical data for use in health economic evaluations

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.*

Within the Health Economics domain, the Capacity and Implementation subdomain in particular intends to draw on information collected in the other domains to develop its tools, while also working with other GeCIP domains to conduct economic evaluations of different service delivery models.

This is indicative of the way that the Health Economics domain as a whole is a keenly sought after partner in providing methodological and subject matter expertise in order to inform planned work streams in other GeCIP domains but also for Genomics England. For instance:

- A specific example of this is the work of a Pharmacogenomics NHSE pharmacogenomics working group, which includes an economic assessment of current and potential tests available and will involve the Stratified Medicine GeCIP domain.
- Another example of required collaboration and drawing on the outputs of other GeCIP domains is also becoming clear: For the above-mentioned work in data-linkage pilot tests on patients across several disease areas, collaboration with the Electronic Health Records domain will be highly beneficial, particularly in sharing expertise and experiences of linking data across different databases
- It is also expected that the domain will work closely with Genomics England to inform decision-making

It is particularly worth noting that, as lead of the Health Economics domain, Sarah Wordsworth has been a very active member of GeCIP, being not only a member of the GeCIP Steering Committee but also of several Rare Disease and Cancer domains. Similarly, Prof. Dyfrig Hughes, another domain member, is also a member of the Stratified Medicine domain (and involved in the above-mentioned pharmacogenomics work), as well as the Musculoskeletal domain.

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

Lead: Alex Thompson (University of Manchester)

There are two areas of focus for education and training (i) to build interest and capacity in the number of health economists working in the evaluation and valuation of genomic-based technologies and (ii) to improve the ability of decision-makers involved in the commissioning of new genomic-based technologies to understand economic evidence in resource allocation decisions. The Manchester Centre for Health Economics has three sources for training in health economics: (i) An MSc course on The Economics of Health and (ii) a module on economic evaluation offered as part of the Masters in Public Health (MPH), delivered using Web-based Learning and (iii) a module on the Economics of Genomics and Precision Medicine as part of a MSc in Genomic Medicine. These courses provide a potential resource for building specific capacity and interest in the economics of genomic-based technologies.

Alex Thompson and Katherine Payne are joint leads on the Economics of Genomics and Precision Medicine. The module teaches the principles of health economic analysis with a focus on developing the skills to critically appraise existing studies from the literature in terms of both quality and applicability to current decision-making. In particular, students are taught how to appraise a model-based evaluation of a new genomic-based diagnostic test, where key evidential gaps are likely to occur, and how genetic and genomic-based diagnostics fit into the current reimbursement and regulatory landscape. Access to this knowledge is also provided on a Continual Professional Development basis with the course being attended in previous years by individuals from the NHS, from the pharmaceutical sector and from other academic institutions. Furthermore, a number of short courses are due to be run over the next year that will provide further training on both methods of economic evaluation and also stated preference methods such as DCEs and best worst scaling. Katherine Payne has also provided two-hours for the MSc in Genetic Counselling and MSc in Clinical Bioinformatics on economic evaluation of genomics.

Sarah Wordsworth is Co-Director of a new MSc in Precision Cancer Medicine at the University of Oxford. The health economic module teaches the principles of health economic evaluation and how to use linked data sources from genomics sequencing programmes. The course is aimed as students from both the UK and internationally. In addition, the Health Economics Research Centre (University of Oxford) has for over 20 years run a one-day course on economic evaluation for NHS staff and also runs a more advanced 3-day course on cost-effectiveness analysis. Finally, both Oxford and Manchester currently have MSc and PhD students pursuing topics in the economics of genomic technologies, which is a process we would endeavour to continue.

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

This domain brings together a highly experienced group of UK and international health economists, who will be supported by clinicians and scientists.

- Domain lead Dr. Sarah Wordsworth is Associate Professor of Health Economics and has over 20 years' experience carrying out health economic evaluations, especially in genomics. She

leads a team of researchers at the Health Economics Research Centre, University of Oxford, who are working on a variety of projects evaluating the costs and outcomes associated with the use of next generation sequencing technologies in the NHS. Sarah has particular expertise in costing methodologies, genomics technologies economic evaluations and preference-based methodologies.

- Subdomain lead Prof. Katherine Payne (University of Manchester) holds expertise in the economics of genomics and precision medicine and development of preference based methodologies.
- Subdomain lead Dr. James Buchanan (Health Economics Research Centre, University of Oxford) holds expertise in the economics of genetic and genomic technologies, micro-costing, modelling and preference-based methodologies.
- Subdomain lead Dr Gurdeep Sagoo (Public Health Genomics Foundation, University of Cambridge) holds expertise in the design and conduct of diagnostic test accuracy reviews, meta-analysis and economic evaluation of genomic technologies.

Other UK and international health economists in the domain and their complementary areas of expertise are:

Padraig Dixon University of Bristol	Economic evaluation and instrumental variables
Martin Eden Manchester Centre for Health Economics, University of Manchester	Evaluation of complex interventions, analysis of individual patient level economic data, valuing non-health outcomes, use of qualitative research methods, stated preference elicitation methods
Patrick Fahr Health Economics Research Centre, University of Oxford	Economics of genetic and genomic technologies, analysis of big data
Jilles Fermont Health Economics Research Centre, University of Cambridge	Economics of genetic and genomic technologies, microcosting, stated preference elicitation methods
Dr Ewan Gray Manchester Centre for Health Economics, University of Manchester	Model-based economic analysis
Dr Sean Gavan Manchester Centre for Health Economics, University of Manchester	Model-based economic analysis
Professor Dyfrig Hughes Bangor University	Economic evaluation of genetic testing in relation to avoidance of adverse drug reactions, and treatments for rare diseases
Dr Jose Leal Health Economics Research Centre, University of Oxford	Evidence synthesis frameworks, individual patient-level and cohort decision modelling
Professor Steve Morris University College London	Economics of using genetic tests for prenatal screening and diagnosis, economic evaluation
Dr Rafael Pinedo-Villanueva University of Oxford	Health economics of rare diseases
Professor Richard Smith Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine	Evaluation of complex interventions, model-based economic analysis particularly in infectious diseases
Alex Thompson Manchester Centre for Health Economics, University of Manchester	Model-based economic analysis, econometric analysis of large datasets.

Professor Adrian Towse Office of Health Economics	Policy issues related to pharmacogenomics and personalised medicine
Dr Caroline Vass Manchester Centre for Health Economics, University of Manchester	Stated preference elicitation methods
Stuart Wright Manchester Centre for Health Economics, University of Manchester	Evaluation of complex interventions, valuing non-health outcomes, use of direct observation methods, stated preference elicitation methods
Professor Lou Garrison University of Washington	National and international health policy issues related to pharmacogenomics and personalized medicine
Professor Maarten Ijzerman University of Melbourne	Personalised medicine, economic evaluation, preference elicitation
Professor Reiner Leidl Institute of Health Economics and Health Care Management, Ludwig-Maximilians-Universität, Munich	Economics of genetic and genomic technologies, model-based economic analysis
Professor Kathryn A. Phillips University of California and Founder / Director, UCSF Center for Translational and Policy Research on Personalized Medicine	Economics of genetic and genomic technologies, with a particular focus on policy issues
Professor Uwe Siebert UMIT, Austria and Harvard University, USA	Economics of genetic and genomic technologies, methods and procedures in health technology assessment
Professor David Veenstra Department of Pharmacy, University of Washington	Decision modelling, economic evaluation of WGS

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.*

Rather than helping clinical interpretation by addressing specific variant interpretation, this domain intends to produce recommendations pertinent to the GMS on where sequencing could be added to patient care pathways in order to maximise patient benefits. One option is to use the technology as soon as a disease or condition is suspected. However, it could be the case that other 'simpler' tests might be best used first, acting as a triage process (similar to current practice). There could be a case for introducing sequencing much earlier in the patient pathway, thus avoiding the 'simpler' tests in the first place, especially if it is likely that most people will ultimately undergo sequencing regardless. Furthermore, it is important to consider how clinicians use WGS information – for example, when do they consider a combination of markers sufficient to guide therapy decisions and what would be the added value of another marker? This lack of "guideline adherence" may be caused by incomplete evidence or different value judgments about the clinical utility of genomic information.

Similarly, it is to be expected that output from this domain will inform the question of whether the provision of information on secondary findings could be considered as a standard part of the patient care pathway in the GMS. Observing secondary findings raises many issues, such as which findings should be reported back to patients, how this should be done, and when to disclose these

results. This will be an important aspect of Validation and Feedback for genomic medicine moving forwards.

To further ensure patient benefit through clinical interpretation, the Health Economics domain also includes designated Clinical and Policy Collaborators, which are:

- Dr Mark Kroese (Director of NICE Diagnostics Programme): Consultant in Public Health Medicine, public health genomics, evaluation of genetic tests (Public Health expert advisor to UK Genetic Testing Network)
- Professor William Newman (Manchester Centre for Genomic Medicine, University of Manchester): Professor of Translational Genomic Medicine
- Liz Ormondroyd (Genetic counsellor, University of Oxford)
- Dr Anna Schuh (Oxford Biomedical Research Centre, University of Oxford and NHS Molecular Diagnostic Centre, Oxford University Hospitals NHS Trust): developing and evaluating new diagnostic tools to improve response prediction in leukaemia and cancer using whole genome technologies
- Dr Ingrid Slade (ETHOX, University of Oxford): Clinical and molecular genetics, public health bioethics
- Dr Jenny Taylor (Oxford Biomedical Research Centre, University of Oxford): Directing translational research programmes in genetics
- Professor Ian Tomlinson (University of Birmingham): Population genetics, particularly bowel cancer

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

The following key outputs are planned from this domain, to benefit the NHS (specifically the Genomic Medicine Service) and thus the healthcare professionals working within it and, ultimately, patients:

- A genomics costs database (GC Database), which would be maintained and updated
- A set of NHS tariffs using information from the GC Database
- Guidelines for reporting economic evaluation in genomic medicine to ensure consistency and quality in economic evaluation in this area as a legacy of the 100KGP
- Guidelines for the design of economic evaluation in genomic medicine to ensure consistency and quality in economic evaluation in this area as a legacy of the 100KGP
- Guidance on whether non-health consequences should be valued using a welfarist or extra-welfarist approach
- Information on how these non-health consequences should be traded-off against health
- Evidence of the preferences of key stakeholders for different genomic tests, and also for alternative forms of service delivery
- Demonstration of methodological and policy approaches to link genomic, clinical and resource evidence generation
- Guidance on current and expected capacity, demand, activity and patient flow to allow the identification and quantification of bottlenecks and their estimated impact on service delivery
- Training and education in the methods used to perform economic evaluation, tailored to the genomics context, for those who will be making policy decisions locally, regionally, nationally and internationally

By producing research output on issues such as how to deal with secondary findings or where in the patient pathway to insert genomic technologies, a wider circle of beneficiaries can be expected to include sectors such as genetic counselling or technology providers.

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?*

There are no imminent plans to commercially exploit research results within the Health Economics domain. However, outputs and findings are likely to be of keen interest to Genomics England Discovery Forum (industry) partners (many of whom have expressed an interest in working with the domain) and are likely to inform Genomics England's own strategy going forward.

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

1. Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics. 2013;14(15):1833-47

2. Annemans L, Redekop K, Payne K. Current Methodological Issues in the Economic Assessment of Personalized Medicine. Value in Health. 2013;16(6, Supplement):S20-S6

3. Rogowski W, Payne K, Schnell-Inderst P, et al. Concepts of 'personalization' in personalized medicine: implications for economic evaluation. Pharmacoeconomics. 2015;33(1):49-59

4. Djalalov S, Musa Z, Mendelson M, Siminovitch K, Hoch J. A review of economic evaluations of genetic testing services and interventions (2004-2009). Genetics in Medicine. 2011;13(2):89-94

5. NHS Reference Costs. 2015; Available from: https://www.gov.uk/government/collections/nhs-reference-costs#published-reference-costs

6. PSSRU. Unit Costs of Health & Social Care. University of Kent, 2014

7. Brouwer WBF, Culyer AJ, van Exel NJA, Rutten FFH. Welfarism vs. extra-welfarism. Journal of Health Economics. 2008;27(2):325-38

8. Smith RD, Sach TH. Contingent valuation: what needs to be done? Health Economics, Policy and Law. 2010;5(01):91-111

9. Payne K, McAllister M, Davies LM. Valuing the economic benefits of complex interventions: when maximising health is not sufficient. Health Economics. 2012:n/a-n/a

10. Flynn TN. Valuing citizen and patient preferences in health: recent developments in three types of best-worst scaling. Expert review of pharmacoeconomics & outcomes research. 2010;10(3):259-67

11. Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. Genet Med. 2008;10(9):648-54. Epub 2008/11/04

12. Payne K, Fargher EA, Roberts SA, et al. Valuing pharmacogenetic testing services: a comparison of patients' and health care professionals' preferences. Value Health. 2011;14(1):121-34. Epub 2011/01/08

Subdomain Outcomes: Detailed research plan

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	

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.*

Valuing new potential genomic diagnostic and stratified treatment strategies within the NHS constitutes a scientific challenge in its own right. For instance, it is currently a common feature of WGS in the clinic that new genomic-based diagnostics, while improving the probability of patients and families gaining a diagnosis, may not offer subsequent treatment options, so that current valuation parameters might need expanding or updating.

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.*

Broadly speaking, there are two types of economic evaluation, cost benefit analysis (CBA) and cost effectiveness analysis (CEA), underpinned by the concepts of 'welfarism' and 'extra-welfarism', respectively. Welfarism stipulates that the value of a technology, intervention or policy can only be assessed in terms of whether it is 'good' for the individuals who represent that society[7]. Applying this approach commonly requires the use of a method called willingness to pay (WTP), often via survey methods, which establishes a monetary valuation of the perceived benefit being attached to the technology. This monetary benefit is then compared with the costs associated with the intervention in question, in cost-benefit analysis (CBA). However, there are very few practical examples of full CBA in healthcare anywhere in the world, which may be a consequence of ongoing methodological challenges related to the monetary valuation of health benefits. There are also concerns regarding the use of WTP, which implicitly incorporates ability to pay, so may lead to resource allocation decisions favouring different socio-economic groups in society[8].

The alternative approach, extra-welfarism, provides the theoretical foundation for the use of CEA in the economic evaluation of healthcare technologies and interventions. In practice, this has led to 'health' becoming the targeted benefit of social decision-making and the use of CEA instead of CBA as the analytical framework of choice. Applying the CEA approach requires a 'global' instrument to describe and value health, which is why the EQ-5D has become the most commonly used measure of health status, recommended by the National Institute for Health and Care Excellence (NICE).

New genomic technologies informed by the 100,000 Genomes Project are likely to take one of two forms: (i) genomic-based diagnostics for inherited rare conditions and (ii) genomic-based stratified treatment strategies. It is likely to be straightforward to value the latter using a measure of health status as there are clear and measurable potential changes in health benefits that can be captured. However, new genomic-based diagnostics, while improving the probability of patients and families gaining a diagnosis, may not offer subsequent treatment options. Consequently, the use of the current NICE economic evaluation approach has been questioned in this context. Some have argued for the use of other methods such as WTP. Others have argued that it is feasible to continue to take an extra-welfarist perspective (consistent with using CEA), but to broaden this beyond the current restrictive definition of health by using the capabilities approach, whereby the value of an intervention is considered to be derived from its impact on individual capabilities (capturing the value of informed decision making)[9].

This subdomain will use exemplars of new genomic-based diagnostics to (1) collate empirical data

to support whether non-health benefits should be considered and paid for by the NHS; (2) understand whether non-health consequences should be valued using (i) a welfarist (WTP) or (ii) extra-welfarist (using an adapted QALY) approach; (3) determine how these non-health consequences should be traded-off against health, and (4) determine how to take account of non-health benefits in the opportunity costs.

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

7. Brouwer WBF, Culyer AJ, van Exel NJA, Rutten FFH. Welfarism vs. extra-welfarism. Journal of Health Economics. 2008;27(2):325-38

8. Smith RD, Sach TH. Contingent valuation: what needs to be done? Health Economics, Policy and Law. 2010;5(01):91-111

9. Payne K, McAllister M, Davies LM. Valuing the economic benefits of complex interventions: when maximising health is not sufficient. Health Economics. 2012:n/a-n/a

Subdomain Stakeholder Preferences: Detailed research plan

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	

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.*

If genomic medicine is to be fully integrated and implemented within the NHS, and in order to inform the evaluation of the outcomes of WGS, it is vital that the preferences of all stakeholders are considered as part of this process

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

This subdomain plans to elicit the preferences of all stakeholders in the process of embedding WGS in the NHS. Three stakeholder groups are particularly important: patients, clinicians and healthcare professionals. It is important to quantify the preferences of these groups for the provision and use of genetic diagnostic risk information from WGS (particularly if this does not have therapeutic consequences), and also their views on the value of stratifying treatments for diseases such as cancer. In addition, it is crucial that we fully understand how these stakeholders would like the future genomic testing service to be delivered.

This subdomain is focused on eliciting the preferences of these key stakeholders using well-established health economic approaches, primarily stated preference valuation surveys. A variety of stated preference survey techniques exist and of these, discrete choice experiments (DCEs) and best-worst scaling may be particularly appropriate in this context[10]. These approaches present participants with choices between hypothetical genomic testing scenarios and can provide information on whether and in what way respondents value genomic testing. Stated preference surveys are particularly useful for eliciting valuations of the non-health outcomes of genomic testing that are not always captured by measures such as the EQ-5D. These non-health outcomes can include the improved certainty of knowing, reassurance and anxiety relief, reductions in the frequency of diagnostic odysseys and healthcare process-related benefits[11]. The valuations that are derived from a stated preference survey for these outcomes can be used to estimate overall WTP for genomic testing, which can be compared with costs in a cost-benefit analysis. Consequently, this subdomain is closely linked with the Outcomes Subdomain, and it is likely that some of the research undertaken to evaluate stakeholder preferences will be used as an input to activities in the Outcomes Subdomain.

The activities in this subdomain will require access to patients across cancer, rare diseases and infectious diseases in order to conduct large-scale stated preference surveys to establish the value that patients place on aspects of testing such as test effectiveness, sensitivity, specificity and the provision of information on secondary findings. The surveys will be designed and conducted with extensive subgroup analysis in mind, given likely differences in risk perceptions and attitudes. Similar surveys will be conducted amongst clinicians and healthcare professionals as evidence suggests that they have very different preferences for the attributes of the tests themselves[12]. These stakeholders will also be surveyed to establish their preferences for different models of service delivery. In these surveys, key questions will include which secondary findings should be returned to patients, what is the range and nature of clinical services that may benefit from the

integration of WGS within diagnostic pathways, and what forms of regulation are needed to ensure that future WGS results are regarded as a sound basis for clinical decision-making?

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

10. Flynn TN. Valuing citizen and patient preferences in health: recent developments in three types of best-worst scaling. Expert review of pharmacoeconomics & outcomes research. 2010;10(3):259-67

11. Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. Genet Med. 2008;10(9):648-54. Epub 2008/11/04

12. Payne K, Fargher EA, Roberts SA, et al. Valuing pharmacogenetic testing services: a comparison of patients' and health care professionals' preferences. Value Health. 2011;14(1):121-34. Epub 2011/01/08

Subdomain Capacity and Implementation Detailed research plan

Full proposal (total max 1500 words per subdomain)	
Title *(max 150 characters)*	

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.*

In order to facilitate the integration of genomic medicine into the NHS by 2017, a greater understanding is needed of how these technologies and their outcomes will impact on demand and capacity both within clinical genetics services and in the wider NHS. At the moment, for instance, cost-based reimbursement for tests and inflexible pricing for companion medicines do not provide sufficient incentive for test developers or stratified medicine manufacturers to invest the resources required to develop and validate genetic tests with an appropriate evidence base, which constitutes an urgent methodological problem.

Research plans. *Give details of the analyses and experimental approaches, study designs and techniques that will be used and timelines for your analysis. Describe the major challenges of the research and the steps required to mitigate these.*

This subdomain will work with other domains and subdomains within and beyond the health economics domain to conduct economic evaluations of different service delivery models. By mapping current and predicted capacity, demand, activities and patient flow, potential bottlenecks in service delivery will be identified and their estimated impact on patient outcomes quantified. Budget impact analysis will also be used to assess the financial implications of more widespread use of genomic technologies throughout the NHS in order to help decisions-makers to better manage health care delivery. Two further key programmes of work within this subdomain are described below.

(i) Incentives for evidence generation: At present, perverse incentives exist in current reimbursement policies for genetic tests and companion medicines. Cost-based reimbursement for tests and inflexible pricing for companion medicines do not provide sufficient incentive for test developers or stratified medicine manufacturers to invest the resources required to develop and validate genetic tests with an appropriate evidence base. Furthermore, as noted in other subdomains, a narrow concept of value is employed in current NICE policies and traditional economic evaluation methods (i.e., focusing on cost offsets and QALYs gained) which does not reflect other potential sources of value that could be derived from genomic technologies e.g. the “value of knowing”. This programme of work will explore the costs associated with generating the evidence that is required to support WGS applications and consider which reimbursement policies could provide the necessary resources.

(ii) Implementation tools for genomic medicine: Policymakers are increasingly expected to base their decisions on a robust evidence base. However, high quality evidence is not always available, preventing informed decision-making. It is also often unclear who is going to offer genetics services. Consequently the provision of transparent evidence on costs and effects could help to guide where resources could be best placed. This programme of work will draw on information collected in the other domains to provide practical tools and policy recommendations to enable policymakers to develop supportive policies and make robust decisions for the implementation of genomic medicine in the NHS.

Data access and security	
GeCIP domain name	[from previous entry]
Project title *(max 150 characters)*	[from previous entry]

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*

☐ *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.