A conversation with clinicians: shaping the implementation of genomics in mainstream medicine
Authors:
Louise Cameron and Hilary Burton

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2 Worts Causeway
Cambridge
CB1 8RN, UK

Tel: +44 (0) 1223 761 900

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Correspondence to:
louise.cameron@phgfoundation.org

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Contents

1. The Genomics Conversation 4
2. Summary of presentations 6
3. Question and answer session 9
4. Group discussions 10

Appendices 17
1. The Genomics Conversation

Genomics England’s engagement programme aims to catalyse discussions with the public and specific expert stakeholders about the potential of genomics and issues likely to arise in its implementation within health services.

The *Conversation with Clinicians* meeting brought together leaders from Genomics England and NHS England with senior clinicians who have an interest or leadership role for genetic medicine within their specialty, many of whom are involved in the PHG Foundation’s [Genomics in Mainstream Medicine](#) initiative. Also joining the discussion were practitioners with more generalist interests within a specialty, and others with an interest in professional development including within the Royal College of General Practitioners (RCGP) and Health Education England (HEE).

The specialties and cross-cutting themes represented in the meeting are below:

**Specialties**

- Cardiology
- Respiratory Medicine
- Gastroenterology
- Diabetes and Endocrinology
- Oncology
- Haematology
- Nephrology
- Ophthalmology
- Paediatrics
- Paediatric neurology
- Neurology
- Dermatology
- Psychiatry
- Microbiology
- Pharmacology
- Clinical genetics
- Pathology
- Public health
- Primary care
- Medical education
The discussion explored the potential of genomics for patients in mainstream clinical disciplines, identifying the barriers and opportunities to implementing this. The results of these discussions will feed into the Genomics England engagement programme to help shape the ‘NHS legacy’ of the 100,000 Genomes Project.

The meeting lasted approximately three hours and took the form of three introductory presentations followed by group work and finally feedback and facilitated discussion. The outline programme is provided in Appendix 2 and the list of participants in Appendix 3.

This report includes:

- Summaries of the presentations from Dr Hilary Burton, chairman of the Genomics in Mainstream Medicine Working Group, Prof Mark Caulfield, Chief Scientist, Genomics England and Prof Sue Hill, Chief Scientific Officer, NHS England. More detailed summaries of these presentations are provided in Appendix 1
- A summary of the question and answer session
- A summary of the group discussion sessions regarding the main opportunities and challenges of implementing genomic testing into routine clinical service
2. Summary of presentations

Dr Hilary Burton, Director, PHG Foundation

Dr Hilary Burton thanked those attending and began by outlining the PHG Foundation's work over recent years, looking at genomic sequencing and its potential clinical applications, particularly in personalised medicine. Initially opportunities were identified to apply genomics within cardiology and ophthalmology, then extending to a broad range of clinical disciplines. This led to the establishment of the Royal College of Physicians (RCP) Genomics in Mainstream Medicine group. The PHG Foundation's 2014 report, Realising Genomics in Clinical Practice looks at the ethical, legal and social issues in delivering genomic medicine, and the 2015 Pathogen Genomics Into Practice report examines the practicalities of delivering next generation sequencing in infectious diseases.

Dr Burton also described one aim of the 100,000 Genomes Project to create a genomic medicine service to transform patient care, and to apply this in routine care settings. Clinicians are vital to realising this vision and the RCP Genomics in Mainstream Medicine group was set up, under the leadership of RCP president, Sir Richard Thompson, to educate clinicians and develop competencies regarding genomic medicine in their specialties. A clinical champions group focusing on education and raising awareness in mainstream disciplines was also established, the steering group for which includes: the Royal College of Physicians (RCP), Royal College of Pathology (RCPath), Royal College of Paediatrics and Child Health (RCPCH) and the Royal College of General Practitioners (RCGP), Health Education England (HEE) and the Clinical Genetics Society (CGS). Introductory resources have been produced which are specialty focused and these are available on the PHG Foundation website.

The purpose of the meeting was to describe the opportunities and barriers to the introduction of genomic testing into routine clinical service and the vital aspects of an implementation programme for genomic medicine by bringing together attendees including genomics enthusiasts drawn from clinical champions, along with other experienced practitioners, covering a large range of disease areas and cross cutting specialties. Dr Burton outlined some of the issues that might form part of the discussions:

• Creating the vision and getting ownership
• Organisation and leadership at the clinical level
• Equity across the whole country
• Genomics at scale, capacity and competence
• Genomics as part of modern diagnostics
• Embedding data collection and sharing
• Making the case for genomic medicine, alongside competing priorities
• Public acceptability
• Potential risks
Probing the 100,000 Genomes Project with Prof Mark Caulfield

Prof Mark Caulfield outlined the aims of the 100,000 Genomes Project, describing how the key elements of the programme fit together, including the Genomic Medicine Centres (GMCs), the sequencing hub run by the Genomics England sequencing partner, Illumina, the Genomics England Clinical Interpretation Partnership (GeCIP) domains, and industry partnerships, and illustrated the flow of samples and data through this structure. He highlighted the importance of the people in the programme, and the need to engage those who are not necessarily involved with genomic medicine on a daily basis, and the critical role of education and HEE in underpinning this capacity.

Providing an update on progress, Prof Caulfield noted that the pilot study has recruited 4800 rare disease patients with over 149 conditions. A small number of diagnoses have so far been returned. In the main study, so far 8500 patients have been recruited with 186 disorders, and a small number of diagnoses returned.

The cancer arm of the programme is progressing more slowly than expected, as the logistics of setting up a system to deliver fresh frozen tissue has proved challenging. The cancer arm is currently focused on this challenge in order to guarantee the supply of material which will return accurate, consistent results. The infectious diseases arm will examine multi-drug resistant strains of TB, and study other microbes in the context of severe response to infection.

Three case studies were described of families who have received a diagnosis as a result of the 100,000 Genomes Project.

Prof Caulfield outlined further developments capitalising on the enhanced genomic and phenotypic data of the 100,000 Genomes Project including a more stratified approach to producing new drugs and administering existing ones, for which the drug discovery platform Open PHACTS will be an important tool. He also described the work of the GENE consortium of 12 pharmaceutical and diagnostic company partners whose aim is to stimulate therapeutic and diagnostic innovation and gain insights into regulatory compliance. Finally he noted some international partnerships which included an agreement with Genome British Columbia regarding data from cancer patients, and work with the Garvan Institute in Australia to create a genomic visualisation tool for potential use in NHS records.

A full summary of Prof Caulfield’s talk can be found in Appendix 1.
A conversation with clinicians

Prof Sue Hill, Chief Scientific Officer, NHS England

Prof Sue Hill began by reiterating the four aims of the 100,000 Genomes Project which are:

- Increased discovery of pathogenic variants, leading to new treatments, devices and diagnostics
- Accelerated uptake of advanced genomic medicine practice integrated into the NHS (mainstreaming)
- Increased public understanding and support for genomic medicine
- To stimulate and advance the UK life sciences industry and commercial activity in genomics

She went on to describe the architecture of the project and how it aligns with other priorities for NHS England such as the Cancer Taskforce recommendations and the UK Rare Diseases Strategy. The dispersed delivery afforded by local delivery partners in the 100,000 Genomes Project is key to ensuring mainstreaming of genomic medicine, and is important in terms of demonstrating the benefits to the NHS England board. Although the project will run into 2018, there is a need to plan now for defining future service provision in 2018-2019.

Prof Hill described the power of whole genome sequencing (WGS) as an enhanced diagnostic/interpretative resource, coupled with analysis of ‘omics’ samples as part of the functional genomics pathway, with the aim of enhancing understanding of translation and expression in individuals. She highlighted the critical importance of linking this sequencing and ‘omics’ data with enhanced phenotypic data, with 283 data fields in the cancer arm and 1100 data fields in the rare disease arm. Capitalising fully on this represents a great challenge for genomic medicine, and has generated innovative ways of working including the use of coding systems with consistent terminology to describe clinical care and barcoding for tracking samples. In terms of interpretation of the sequence data, a pivotal element of the project involves the appraisal of data curation systems, with an expanded bioinformatics workforce required in the future to provide this service.

The 100,000 Genomes Project is central to delivering NHS England’s Personalised Medicine Strategy, which will rely heavily on genomic, functional genomic and phenotypic data to identify more individualised approaches to care. Prof Hill outlined the clinical areas where personalised medicine is being prioritised including cancer, diabetes, learning disabilities, mental health and dementia, cardiovascular disease, warfarin and other adverse drug reactions, maternity and children, and rare disease. It is hoped that this commitment will support substantial developments in pharmacogenomics, including identifying new drugs, repurposing existing drugs and tailoring prescription practices. It is also hoped that the genotypic and phenotypic insights from the 100,000 Genomes Project will enable earlier detection of disease which, coupled with more targeted therapies, should drive improved outcomes.

Prof Hill ended with a summary of aims for the project and the implementation of genomics into the NHS over the next 10 years including: development of the genomic laboratory infrastructure, new pathways and models of care, WGS being applied in routine care, full deployment of the functional genomics pathway, optimisation of medicines and other therapeutics, closer alignment of clinical research and research, new partnerships with industry, and greater public understanding regarding genomics.

A full summary of Prof Hill’s talk can be found in Appendix 1.
3. Question and answer session

A question was asked regarding the significance of genomic sequencing for infectious diseases within the 100,000 Genomes Project. The difficulties of securing resources to provide next generation sequencing services in microbiology laboratories for NHS patients were highlighted. Prof Hill explained that microbial sequencing was not a priority for Genomics England, which was focussing on human genome sequencing but that it should be included. She commented that Public Health England was moving at pace with microbial genomics, but that NHS laboratories are behind the curve. The implementation of next generation sequencing thus represents a parallel piece of work, and the application of genomics with regard to antimicrobial resistance may act as a lever for implementing a more systematic approach in the NHS.

The issue of targeted medicines and companion diagnostics was discussed, and Prof Hill explained that a multi-faceted approach would be taken depending on the clinical scenario, with the continued use of companion diagnostics in some circumstances, e.g. to support point of care testing in primary care, and dropping their use in other situations where this would not be the most efficient approach.
4. Group discussions

The participants were split into four groups and asked to consider the opportunities and barriers relevant to the introduction of genomic testing into routine clinical service. Several key themes emerged from the discussions, which are summarised below.

The majority of the groups’ discussions focused on the barriers; opportunities were mainly considered in terms of the potential benefits from genomics rather than wider contextual aspects.

Potential benefits, and methods to capitalise on them

Diagnostic and therapeutic areas

It was felt that the diagnostic benefits would be most significant for rare disease patients, patients with a significant family history of certain disorders, and patients with multiple morbidities managed under a number of clinical specialties, where a unified diagnosis would be valuable. Genomics could provide benefit in infectious disease medicine to determine resistance to antimicrobial therapies and the investigation of outbreaks. However, the utility in these contexts is inextricably linked to the turnaround time. There was some optimism that genomics might provide a tool to tackle some of the major health burdens such as obesity and diabetes.

Near patient care and responsiveness

If genomic information is available at the point of care in the form of pre-emptive clinical testing, as described in the paper by Bielinski et al., this could be successful in improving outcomes. For example, clinicians would then have immediate information to inform drug choice. It was felt that such prospective testing, with data in GP records, could ultimately lead to more effective prescribing, and would have a huge impact if applicable to drugs for common, chronic disorders such as dementia, asthma, or depression.

**Improved patient care and outcomes**

WGS could help to reduce the diagnostic odyssey currently faced by some patients with serial testing and multiple appointments in the search for a diagnosis. Even where a treatment is not available, the information from having a genetic diagnosis may be valuable, for example in assisting patients to access support groups. Genomic testing would bring the benefits of fewer tests - for example reducing discomfort or exposure to radiation from CT scans, improve prescribing practice and reduce adverse drug reactions. Bringing together clinical specialties through the common thread of genomics may help to improve care experienced by patients. Genomics could also act as a catalyst for more generalised improvements in data integration. Even for patients for whom there is currently no treatment available, identifying potential therapeutic targets may yield downstream benefits.

**Reduced costs**

Genomic medicine may yield reduced costs from more efficient treatment, although the number of patients and therefore the scale of economic benefits is still difficult to quantify.

**Repurposing drugs**

Genomic data may be used, especially in conjunction with the functional genomics pathway, to identify targets for repurposing drugs.

**Applications of a multiplex technology**

WGS represents one assay for potentially multiple uses, including, for example, drug response and likelihood of adult onset acute or chronic conditions, which could facilitate a range of measures to mitigate risks.
Potential barriers and what is needed to overcome them

**Complexity**

The sheer complexity of delivering genomic medicine was acknowledged at the outset. This is an emerging technology and clinician researchers are only now learning how to use it. Nevertheless the vision is to integrate it widely into clinical medicine across a range of specialties within the next few years and at scale. In every area there will be challenges: in understanding clinical applicability; gathering evidence; making arguments for cost-effectiveness; commissioning and moving of budgets; and a range of practical problems. At the forefront of these practical problems will be physician education. Education of the public and a number of regulatory and ethical issues will also need to be addressed and good practice developed. Overall the view was that the health service was currently ‘a million miles’ away from being able to deliver genomic medicine.

**Clinical applicability of genomic testing**

One of the major challenges for clinicians will be in knowing where genomic testing has been useful for their patients. At present, patients who are chosen for testing are often those where there is a strong conviction that they have a rare disease which has a genetic aetiology but no underlying molecular diagnosis has been found. Most clinicians, especially GPs who see few patients with rare conditions, will need clear referral criteria for conditions with less distinct phenotypes. This will ensure they are able to take advantage of the available testing for monogenic disorders, where much progress has been made and also that they gain access to genome sequencing at the appropriate stage.

**Commissioning**

Commissioning decisions require a certain form and type of evidence and it is important that the details of this are clear before plans are put in place for evaluation. NHS England could help in this regard and should do so at an early stage. This may work well for rare disease where NHS England has experience of specialised commissioning but there is no clear structure for approving innovative testing or pathways for more common disease, or common presentations of rare disease. The fact that CCGs have limited control of clinical practice could be problematic.
Evidence of benefit

There is a need to show clear evidence of benefit from genomic testing in order to persuade clinicians to use these tests and commissioners to fund them. This could be challenging and the evidence arising from the 100,000 Genomes Project may not be the most helpful in this particular context. This is in part due to the fact that the project is gathering genomic information on some very heterogeneous disorders such as epilepsy. Detailed work with sufficient cases and including examples across the whole range will need to be undertaken before it can be established whether there are benefits of testing for the group as a whole or just some subgroups.

Furthermore, within any one specialty or group, genomic testing is only one tool within a whole diagnostic and therapeutic repertoire and it will be important to show demonstrable benefits for this testing modality potentially within an integrated system. In view of the multiplicity of tests, conditions and circumstances under consideration, it seems clear that a more streamlined process for gathering and providing evidence of benefit would help clinicians to argue the case for genomic testing. Importantly there is also concern at the lack of knowledge around predicting risk for low penetrance variants, particularly for some late onset disorders.

Budgetary issues

In relation to the question of commissioning and provision of testing there were concerns that current budgetary silos would preclude the movement of testing from one part of the service to another and the new provision of testing; one example of this was the provision of new point of care pharmacogenomics testing which might fall directly on GPs. The full cost would be alleviated to some extent if ‘pre-emptive testing’ were undertaken so that sequence information was already stored and only the relevant interpretation had to be undertaken. As well as the direct costs of this there will also be increased workload around decision making for testing and discussions of interpretation which would be unlikely to attract attendant funding. All of the potential increased cost will make it very difficult for cash-strapped CCGs to prioritise genomic medicine.
Changes to care pathways

Assuming evidence of the benefits of testing becomes clear it is likely that pathways of care will change. With different testing being undertaken, potentially under new criteria (and therefore for a different group of patients) at different points in the pathway it will be essential that proper focus is given to remodelling the pathway rather than simply bolting additional aspects onto pre-existing services. Thorough work must be done on this with good stakeholder involvement so that clinicians can be confident that the new approach ‘will not cause chaos’ and to convince them that the changes will be worthwhile.

Healthcare professional education

With the exception of such areas as cancer multi-disciplinary teams (MDTs) few clinicians are currently exposed to genetic medicine on a daily basis. Professionals regularly do not understand the basics of molecular testing and many find the terminology hard to follow. Those who have not been involved in developments such as the 100,000 Genomes Project will not readily pick up the aspects of new practice expected of them.

At present many clinicians are likely to stick to behaviours on testing instilled in medical school: ‘don’t test if you don’t know what you’ll do with the result.’ Education in genomics is thus critical to ensure clinicians have the knowledge they need to integrate testing into their own practice and to be involved in new approaches to care. This will need to include various modes for delivery of educational resources, which should also include methods for assessment.

It was thought that genomic medicine is not currently well integrated in the curriculum and there was acknowledgement that changes will take some time. Nevertheless there is currently a window of opportunity to train doctors with a good understanding of the molecular and cellular basis of disease.

The key changes suggested included better representation of rare disease, and a focus on genomics beyond modes of inheritance, to include practical skills needed to identify patients who may benefit from testing. Even so, with a vast amount of specialist education required to cover the relevance of genomics to disease in every clinical area, it was clear that such education was beyond the capacity of clinical genetics to deliver. A practical step forward would be to designate an educational lead in each disease area and to continue to support these individuals through the dedicated Genomics in Mainstream Medicine working group.
A number of practical problems need to be addressed if genomics is to be introduced more widely into medical practice. These include a set of issues related to service structure and the overall capacity and capability of vital service components. Issues include:

» Securing the correct resources on the ground in terms of trained personnel and appropriate facilities when new pathways are introduced. This was described graphically in a well-studied pilot to introduce genetic testing in relation to anticoagulation with warfarin into a routine service setting.

» The lack of skills in family history taking, which is vitally important e.g. in familial cancer and the difficulties of addressing this adequately in the context of routine clinics.

» The lack of bioinformatic support which means that panel results may therefore take a long time to be returned.

» The need to establish responsibility for the interpretation of genomic data, and ensuring systems provide information which is clear for the referrer to interpret.

» The interpretation of variants of uncertain significance (VUS) which needs to be streamlined, rapid and clinician friendly.

» The need to strengthen clinical genetics to support all WGS being undertaken.

» The need for systems to ensure WGS is done once and the assay is not inadvertently repeated by a different part of the service.

» Completing lengthy proformas for phenotypic features. This was an issue particularly where the basis of testing (whether research or clinical) was unclear as is currently the case. It was felt that an excessive burden of phenotypic data collection was out of proportion to the limited value that the individual patient would derive. Although some physicians were content to emphasise the value of research in the context of the current programme, this may not be sustainable as genomic testing becomes more routine in the health service.

» Once patients are in the system there will also be questions of how and when to revisit a diagnosis (or a lack of diagnosis) as the status of some mutations in terms of pathogenicity is fluid, and evolving over time in light of enhanced data. Clinicians will need guidance on how and when to re-contact patients in the light of new knowledge.

» Dealing with secondary findings, as it is potentially costly to counsel patients for these and it may also be costly to refer them for subsequent advice.

» Attendant issues such as lack of investment in other allied areas such as pathology and bioinformatics with which genomics will interface.

» The need to link up pathology with wider clinical disciplines, to ensure that results are available to all areas of the service providing clinical care to the patient.
A conversation with clinicians

**Regulatory and ethical issues**

In the discussion this largely focused on the need for regulation to be proportionate. For example, with regard to theranostics, it was questioned whether the Medicines and Healthcare products Regulatory Agency (MHRA) should be licensing this or whether there would eventually be a need for a committee to deal with medicines and diagnostics. Discussions on ethical issues focused mainly on near patient testing, and ethical aspects of any test which may reveal relatedness. Direct to consumer testing was also raised as a concern, and how to counsel patients who may present with the findings to their GP. The impact on insurance was also mentioned as a concern of patients who are entering into a genetic testing programme.

**Public education and hype**

An expanded programme of public education would be important to create realistic expectations about the capability of genomic testing and to avoid disillusionment and loss of public support. People may, for example, be afraid of receiving positive results, especially if these are incidental findings, or may expect to receive prognostic information as part of a new genetic diagnosis. Sometimes they will be disappointed that a much hyped test did not provide them with any answers. Increased understanding of genetic testing could facilitate easier discussions and disclosure of results and there should be a realistic framing of the benefits and the possible harms or negative consequences.

It is also necessary to be realistic about the potential for scientific discoveries to eventually make it to the clinic. For example, despite the excitement surrounding drugs based on genomic findings, it is important to recognise that many are very expensive and may not be approved by NICE. In cancer treatment, despite scientific breakthroughs, trials may not demonstrate the level of clinical utility and health economic benefits needed to persuade commissioners and effect changes in clinical management.

It was felt that benefits may lie in more ‘nuanced’ mainstreaming. For example, in cardiology, the benefits may not be seen by expanding genomic medicine right across mainstream cardiology, but by focusing the expansion in specific clinical subdomains concerned with rare inherited cardiac disorders such as arrhythmias or cardiomyopathies.

When considering the best approach to public education it may also be useful to start by advocating for the potential in areas with clear examples of clinical utility and cost benefits, such as pharmacogenomics, or in areas of NHS priority such as obesity and where a targeted approach could focus on those most seriously affected.
Appendices

Appendix 1: Presentation summaries in full

Prof Mark Caulfield
Chief Scientist, Genomics England

Introduction

Prof Mark Caulfield thanked the audience for attending, and for sharing their thoughts on how to shape the application of genomics in mainstream medicine.

He reiterated the aims of the 100,000 Genomes Project mission: an NHS translational programme to sequence 100,000 genomes from NHS patients with rare disease and cancer and to undertake sequencing in infectious disease, so that the UK are world leaders in genomic medicine. The project aligns the NHS with academic expertise in universities to recruit patients, analyse results, publish data and drive this into clinical practice, with the ultimate aim of presenting the case for commissioning WGS-based diagnostics to NHS England.

Elements of the programme

Thirteen Genomic Medicine Centres (GMCs) ensure equity of access across England, with Scotland, Northern Ireland and Wales soon to join the programme to provide UK-wide access. All conditions in the programme have been nominated by the NHS or researchers, or through industry partners, who have suggested eligibility criteria and helped devise the model for data collection.

Interpretation of the sequencing data returned is the responsibility of numerous condition-specific and cross-cutting GeCIP domains, drawing in expertise from universities and the health service, with over 2,400 individuals involved at 300 institutions in 24 countries. This expertise has been critical to influencing both the pilot study and the main 100,000 Genomes Project to ensure the best recommendations are made to the NHS regarding implementation. The Sanger Institute in Hinxton houses the sequencing hub, with 15 XTen sequencers, run by the Genomics England sequencing partner Illumina, chosen as the only company capable of operating at the scale required.

Industry partnership has been sought early on to shape the process, to foster academic-industry partnerships, and gain insight into regulatory compliance, and 12 pharmaceutical/diagnostic partners are involved in a precompetitive consortium.
Aside from the infrastructure, of key importance are the people in the programme, and support from those who are not necessarily engaged in genomic medicine on a daily basis. Education plays a very important part in building capacity, and so collaboration with HEE is critical.

The flow of samples and data in the 100,000 Genomes Project is shown in the schematic below.

**Figure 1**

Genomics England – The Big Data Potential

Update on progress

The semi-automated pipeline has taken around 18 months to build, and should be a legacy for use beyond the 100,000 Genomes Project. Sequencing is running faster than the flow of samples, so Genomics England are examining enrolment, particularly focusing on rare disease. Some diagnoses are being returned but not at the desired pace.
The need to standardise data collection is key, and human phenotype ontology terms have been used to describe clinical features and tests. Open Clinica, adopted because it would incur no cost to the NHS in an implementation context, has been used to input this data but this has not worked as well as hoped.

**Pilot study**

The sequencing of pilot study samples is complete and the results are beginning to be analysed with the pilot sites. With the aim of growing a cadre of genomic medicine professionals, clinicians plus a group of 60 students have recruited 4,800 patients, covering over 149 conditions. Over 56,000 human phenotype ontology terms have been recorded. The data set is further enriched by the inclusion of data on 270,000 hospital episodes: 13,000 A&E, 37,000 in-patient care episodes, and the remainder out-patient episodes, highlighting the high cost to the NHS of caring for these patients, who may not receive a genomic diagnosis in their lifetime. The pilot study has only returned a small number of diagnoses so far. Of these diagnoses, 25% were known pathogenic variants, 25% were highly promising expected pathogenic variants, and 50% variants of uncertain significance (VUS).

**Main study**

8,500 mainly rare disease patients have been recruited with 186 disorders and a small number of diagnoses have been returned.

**Cancer genomics**

Work on the cancer programme is progressing slower than hoped. The key challenge is to create a system that can use fresh frozen tissue as opposed to formalin fixed tissue (which cannot be used in a clinical setting because of analytical problems with variable GC/AT dropout). Genomics England are evaluating alternative fixatives, but are concentrating primarily on establishing a pipeline using fresh frozen tissue. Such an undertaking is logistically challenging but important to establish a nucleic acid friendly approach. Therefore the cancer pilot programme is focusing on guaranteeing an improved product which is suitable for sequencing. The subsequent plan was outlined with year 1 focusing on the logistics of supplying fresh frozen tissue, year 2 in which people can nominate small experimental medicine studies and year 3 where it is hoped to run larger multi-arm or basket trials comparing medications in patients.

**Infectious diseases**

This strand of the 100,000 Genomes Project is focused on multi-drug resistant TB strains and TB sequencing, working with PHE, sequencing 3,000 multi-drug resistant TB cases, with a Wellcome Trust award to support the formation of a global registry of TB resistance. The infectious diseases strand will also examine variations in the host genome associated with severe response to infection.
Prof Caulfield described families who had benefited from receiving a diagnosis from the 100,000 Genomes Project, and this is summarised below.

**Examples of families who had received a diagnosis from 100,000 Genomes Project**

**Developments**

It is hoped that the 100,000 Genomes Project will support a more stratified approach to producing new drugs and administering existing ones. Open PHACTS, an Innovative Medicines Initiative, will be used for this purpose. This will assess proteins as potential drug targets, look at chemical signatures and look for drugs which already exist which may be of use, hopefully leading to Phase I and Phase II trials, looking at novel and repurposing targets and examining stratified approaches to drug treatment.

International partnerships are evolving, including an agreement with Genome British Columbia who aim to put the genomic data from 4.5 million patients with 20,000 incident cancers into the 100,000 Genomes Project. Work is also ongoing with the Garvan Institute in Australia to look at creating a genomic visualisation tool to form part of an NHS genomic data record. Collaborative work with groups in Japan is also under discussion.

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**Case one involved a family** with inherited kidney disease. A known pathogenic mutation was found and validated, which prior tests had not identified. This was fed back to the family by the referring GMC.

**Case two involved a family** with a child with developmental delay and seizures which were unresponsive to anti-epileptics. Various tests had failed to reveal a diagnosis and the patient was recruited to the 100,000 Genomes Project through SWAN (syndromes without a name), which revealed a mutation in the glucose transporter 1 gene. This has informed the patient’s treatment and impacted on the seizures.

**Case three involved a family** whose child died at four months from severe immunodeficiency and initial tests did not reveal a diagnosis. DNA from the child was sequenced with consent from the parents, and a mutation in the B12 transport protein gene was found. The NHS laboratory validated this which has allowed testing of a sibling at birth who is also affected, but it is hoped that in starting intervention with high B12 dose at the earliest opportunity, this may help to alleviate symptoms.
**Prof Sue Hill**  
*Chief Scientific Officer, NHS England*

**Introduction**

Prof Sue Hill began by thanking the PHG Foundation for the invitation to speak at the Genomics conversation event, and thanked Mark Caulfield for his leadership of the 100,000 Genomes Project, noting that clinicians and the NHS have remained at the centre of the project, and the planning of future services from the start. Prof Hill also thanked the attendees who are working to ensure the aims and objectives of the project are delivered.

She reiterated the four aims of the 100,000 Genomes Project as outlined in the slide below.

**Figure 2**

**Aims of the 100,000 Genomes Project**

- **Major legacies for patients, the NHS and the UK economy by 2017**
  - Increased discovery of pathogenic variants leading to **new treatments, devices and diagnostics**
  - Accelerate uptake with advanced genomic medicine practice **integrated into the NHS**
  - Increase public understanding & support for genomic medicine
  - Stimulate and advance UK life sciences industry and commercial activity in genomics

**Aligned with NHS strategies**

(long term) **Embed the benefits of genomic medicine across mainstream NHS care esp. through Personalised Medicine**
Project architecture

The project was set up with the NHS delivering its contribution through a highly defined scientific project but during routine care, which brings challenges and opportunities. There are challenges associated with delivering this within routine care appointments, but opportunities to start thinking about mainstreaming from the very beginning. NHS England view the 90,000 genomes contracted from the Genomic Medicine Centres (GMCs) as a step on the journey towards delivery of genomic technologies for the 55 million UK population, and this was a topic of discussion with the NHS England board recently. The original aim was to deliver the project by 2017, but due to challenges outlined, particularly with the cancer arm of project, the project will run into 2018.

The target is to deliver services in the financial year 2018-2019, and therefore there is a need to plan for the future now. The project is helped by being aligned with other NHS strategies, notably the Cancer Task force recommendations, and the UK Rare Diseases Strategy, and demonstrable benefits in this area will attract money for implementation in 2018/19.

The challenge with mainstreaming goes beyond the medical profession; there is a need to consider all healthcare professionals in the 1.3 million workforce. For example, in the cancer programme, it is important to develop cancer nurse specialists, but also to engage managers and commissioners to effect mainstreaming. To ensure equitable access to genomic medicine, the 13 GMCs were created as lead organisations who then work with numerous local delivery partners (LDPs), expecting to total 80-100 by the end of the project. This infrastructure engenders confidence in the NHS England board with regard to mainstreaming, further strengthened by facilitation through local Academic Health Science Networks, and built on the long history of genetic laboratories and clinical genetics services in the NHS, stretching back to the 1960s.

Enhanced diagnostic/interpretative resources

WGS represents a step change in the diagnostic information available; current diagnostic approaches examine single genes, panels of genes, and in some cases the whole exome and this needs to be utilised in the most appropriate method in clinical care.

Omics samples

Samples are being collected now to allow analysis of the functional genomics pathway, which will allow understanding of translation and expression in individuals. This is critical to thinking about drug action, and opens up the possibility of real time monitoring.

Phenotypic data

Linking phenotypic data with genomic data is critical to interpretation, and the 100,000 Genomes Project includes 283 data fields in the cancer arm and 1,100 data fields in the rare disease arm. To properly capitalise on this resource requires unparalleled developments in NHS data and informatics, and has driven the use of SNOMED-CT healthcare coding system and tracking samples through GS1 barcoding, which allows for greater data extraction and interoperability.
Methods for interpretation

The challenge of interpretation is the huge amount of data, and its continual evolution. Systems need to be able to interpret the data both for individuals and across populations or within disease groups, and therefore a range of analytical systems are being assessed for data curation. Looking to future developments, a new bioinformatics workforce is needed to understand the use of data and its predictive value, and innovation in the form of machine learning applications may prove useful.

Key observations

Establishing proficient operating models across geographies brings with it the challenges of ethics, establishing informed consent, maintaining patient participation, and streamlining care pathways. It is reliant on proficient structures for the collection of data and samples for clinical and research use.

Standardisation is important, particularly for laboratory processes, and this has proved especially relevant in the handling of fresh frozen tissue for the cancer arm of the project. Standardisation of models of care is important and this has demonstrated to NHS England how the project can lead to consolidation of some pathways so that services can operate at the correct level of aggregation.

• Data is integral to the project which aims to create a legacy of routine clinical care data collected for research or work with industry
• Multi-disciplinary working is evident in the form of genomic MDTs operating for rare disease and cancer. This pooling of expertise is not just concerned with the return of results, but really bringing people together to manage genomic investigations
• Clinical leadership is very important and the most successful GMCs have demonstrated responsibility distributed across LDPs

Personalised medicine and pharmacogenomics

The 100,000 Genomes Project should embrace the ‘4Ps’ of personalised medicine:

• Prediction
• Precise diagnoses
• Personalised and targeted interventions
• a more Participatory role for patients

From now until 2020, a raft of genomic technologies is needed to integrate rapid near patient testing, markers and therapies, particularly theranostics (testing tightly linked to choice of a particular drug treatment), and robotic molecular platforms to deliver economies of scale.
This activity will be shaped by:

- The evidence base for utility
- Responsiveness and turnaround time of results in a dynamic clinical setting
- Informatics and analytical platforms
- Use of functional genomics to determine drug selection
- Ongoing monitoring of patients

In September 2015 NHS England approved the Personalised Medicine Strategy and the legacy of the 100,000 Genomes Project is embedded in this strategy. This will draw on existing laboratory infrastructure, cutting edge diagnostics, clinical and patient data, to ensure these resources don’t remain compartmentalised. The strategy builds on all emerging technologies, recognising the utility of a range of clinical genome analysis, from WGS right through to single gene analysis. This must be combined with the functional genomics pathway, in terms of expression and interaction with medicines, and needs to be integrated with digital health apps, functional diagnostics and phenotypic characterisation, which may also rely on patient generated data.

In order to achieve this a number of developments are needed, including:

- Informatics resources
- Policy and system alignment e.g. the regulatory environment in which genomics operates
- A new framework for commissioning structures right through from CCGs to highly specialised commissioning which must be aligned with the new genomic medicine
- Clinical leadership is needed to drive genomic medicine through and embed this in new clinical care models
- Broad access. It is important that this is not limited to deployment of big platforms in a small number of centres. Point of care testing and other technology is necessary to bring this closer to patients

The following areas, linked to NHS clinical priorities, are being prioritised in relation to personalised medicine: cancer, diabetes, learning disabilities, mental health and dementia, cardiovascular disease, warfarin and other adverse drug reactions, maternity and children, and rare disease.
Pharmacogenomics

The NHS spends £13 billion on drugs and £8 billion on diagnostics annually. Efficacy rates for prescribed drugs may only be around 30-60% and 1 in 15 hospital episodes are related to adverse drug reactions. Therefore there is room for improvement by making these decisions more scientifically using individual parts of the functional genomics pathway and looking at tissue and organ function, and tying in environmental factors as well as known drug responses. These approaches therefore aim to achieve horizontal integration across organ and body systems as well as vertical integration of a more scientific approach to diagnostics, with data critical to supporting this. The aim is therefore to repurpose existing medicines, guide the use of expensive targeted medicines, and also to look at non-pharma interventions much earlier in the care pathway. It is hoped the ongoing conversation with the pharmaceutical and medical technology industry should lead to new discoveries and allow a more stratified approach to risk identification.

Earlier disease detection

It is hoped that insights into the underlying cause and incidental findings could be used to support diagnosis of disease at an earlier stage, perhaps two to five years earlier. The aim is to improve outcomes by coupling this with the use of more targeted therapies.

Aims for the next 10 years

The aims for the project and beyond over the next 10 years were summarised in figure 3.
Over the next 10 years…

The introduction of genomic medicine – particularly to inform the personalisation of treatment – is the most significant initiative to shape the future delivery of NHS care.

Over the next 10 years this will be seen through:

• Genomic laboratory infrastructure and centres of excellence
• 100,000 Genomes Project informing new pathways and models of care
• WGS applied routinely and in other clinical conditions
• Functional genomic pathway fully deployed (in real time care and also for monitoring)
• Medicines and other therapeutic interventions optimised
• Closer alignment between clinical practice and research for mutual benefit and improved outcomes for patients
• New partnerships with industry
• Greater public understanding of the impact and value of genomics
### Appendix 2: Meeting programme

**A conversation with clinicians: shaping the implementation of genomics in mainstream medicine**

*In collaboration with Genomics England*

<table>
<thead>
<tr>
<th>British Medical Association, 7 June 2016</th>
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<tbody>
<tr>
<td>13:00-14:00</td>
<td><strong>Registration and networking lunch</strong></td>
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<tr>
<td>14:00-14:15</td>
<td><strong>Welcome and overview</strong></td>
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<tr>
<td></td>
<td>Dr Hilary Burton</td>
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<tr>
<td></td>
<td>Director, PHG Foundation and Chair, RCP Working Group on Genomics in Mainstream Medicine</td>
</tr>
<tr>
<td>14:15-14:30</td>
<td><strong>Introduction to the 100,000 Genomes Project</strong></td>
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<tr>
<td></td>
<td>Prof Mark Caulfield</td>
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<tr>
<td></td>
<td>Chief Scientist, Genomics England</td>
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<tr>
<td>14:30-14:45</td>
<td><strong>Integration of genomics into NHS services</strong></td>
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<tr>
<td></td>
<td>Prof Sue Hill</td>
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<tr>
<td></td>
<td>Chief Scientific Officer, NHS England</td>
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<tr>
<td>14:45-15:05</td>
<td><strong>Q &amp; A</strong></td>
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<tr>
<td>15:05-15:20</td>
<td><strong>Break</strong></td>
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<tr>
<td>15:20-16:00</td>
<td><strong>Breakout session</strong></td>
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<td></td>
<td>What are the main opportunities and barriers to the introduction of genomic testing into routine clinical service?</td>
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<tr>
<td>16:00-16:40</td>
<td><strong>Group discussion</strong></td>
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<td>What will be vital aspects of an implementation programme for genomic medicine?</td>
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<tr>
<td>16:40-16:45</td>
<td><strong>Summary &amp; close</strong></td>
</tr>
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## Appendix 3: List of participants

<table>
<thead>
<tr>
<th>Delegates</th>
<th>Position/Institution</th>
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<tbody>
<tr>
<td>Corinna Alberg</td>
<td>Project Manager (Public Health), PHG Foundation</td>
</tr>
<tr>
<td>Dr Martin Allen</td>
<td>Consultant Physician (Respiratory Medicine), University Hospitals of West Midlands</td>
</tr>
<tr>
<td>Dr Jeffrey Aronson</td>
<td>Consultant Physician &amp; Clinical Pharmacologist, Nuffied Department of Primary Care Health Sciences</td>
</tr>
<tr>
<td>Dr Shehla Baig</td>
<td>General Practitioner &amp; Senior Lecturer in Medical Education St George's University of London</td>
</tr>
<tr>
<td>Dr Michelle Bishop</td>
<td>Education Development Specialist, Health Education England</td>
</tr>
<tr>
<td>Prof Maria Bitner-Glindzicz</td>
<td>Prof of Clinical &amp; Molecular Genetics, UCL</td>
</tr>
<tr>
<td>Dr Nick Brown</td>
<td>Consultant Medical Microbiologist, Addenbrookes Hospital &amp; Public Health England</td>
</tr>
<tr>
<td>Dr Hilary Burton</td>
<td>Director, PHG Foundation</td>
</tr>
<tr>
<td>Louise Cameron</td>
<td>Project Manager (Science), PHG Foundation</td>
</tr>
<tr>
<td>Prof Mark Caulfield</td>
<td>Chief Scientist, Genomics England</td>
</tr>
<tr>
<td>Dr Ellen Copson</td>
<td>Honorary Consultant in Medical Oncology, Cancer Research UK &amp; The University of Southampton</td>
</tr>
<tr>
<td>Prof Ian Cree</td>
<td>Honorary Prof of Pathology, University Hospitals Coventry &amp; Warwickshire, Visiting Prof at Coventry University</td>
</tr>
<tr>
<td>Dr Rajith de Silva</td>
<td>Consultant Neurologist, Queen's Hospital</td>
</tr>
<tr>
<td>Maxine Foster</td>
<td>National Programme Manager, Genomics Education Programme Health Education England</td>
</tr>
<tr>
<td>Dr Tom Fowler</td>
<td>Deputy Chief Scientist, Genomics England</td>
</tr>
<tr>
<td>Dr Neil Gittoes</td>
<td>Consultant Endocrinologist and Associate Medical Director, Queen Elizabeth Hospital Birmingham</td>
</tr>
<tr>
<td>Dr Andrew Grace</td>
<td>Consultant Cardiologist, Papworth Hospital</td>
</tr>
<tr>
<td>Dr Judith Hayward</td>
<td>General Practitioner with a Special Interest (GPwSI) in Genetics, The Yorkshire Regional Genetics Service</td>
</tr>
<tr>
<td>Prof Sue Hill</td>
<td>Chief Scientific Officer, NHS England</td>
</tr>
<tr>
<td>Prof Bronwyn Kerr</td>
<td>Consultant Clinical Geneticist, Manchester Centre for Genomic Medicine</td>
</tr>
<tr>
<td>Clinician</td>
<td>Institution</td>
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<tr>
<td>Dr Maria Kinali</td>
<td>Consultant Paediatric Neurologist &amp; Honorary Senior Clinical Lecturer Chelsea and Westminster Healthcare NHS Fdn Trust, Imperial College London</td>
</tr>
<tr>
<td>Dr Mike Knapton</td>
<td>General Practitioner &amp; Associate Medical Director, British Heart Foundation</td>
</tr>
<tr>
<td>Dr Andrew Latchford</td>
<td>Consultant Gastroenterologist, St Mark’s Hospital and Academic Institute</td>
</tr>
<tr>
<td>Prof Irene Leigh</td>
<td>Prof of Cellular &amp; Molecular Medicine, University of Dundee</td>
</tr>
<tr>
<td>Prof Hugh Markus</td>
<td>Honorary Consultant Neurologist, University of Cambridge</td>
</tr>
<tr>
<td>Dr Gautam Mehta</td>
<td>Consultant Gastroenterologist and Hepatologist, UCL Hospital</td>
</tr>
<tr>
<td>Dr Sophie Molloy</td>
<td>Consultant Neurologist, Imperial College Healthcare NHS Trust</td>
</tr>
<tr>
<td>Dr Jiten Morarji</td>
<td>Ophthalmology, Specialist Trainee, Manchester Royal Eye Hospital</td>
</tr>
<tr>
<td>Prof Ruth Newbury-Ecob</td>
<td>Consultant Clinical Geneticist, University Hospitals Bristol</td>
</tr>
<tr>
<td>Vivienne Parry</td>
<td>Head of Engagement, Genomics England</td>
</tr>
<tr>
<td>Prof Sir Munir Pirmohamed</td>
<td>Head of Molecular &amp; Clinical Pharmacology, The Wolfson Centre for Personalised Medicine, Liverpool University</td>
</tr>
<tr>
<td>Dr Imran Rafi</td>
<td>General Practitioner &amp; Chair Royal College of Physicians Clinical Innovation and Research, St George’s University of London</td>
</tr>
<tr>
<td>Dr Tristan Richardson</td>
<td>Consultant in Diabetes &amp; Endocrinology, Royal Bournemouth Hospital</td>
</tr>
<tr>
<td>Prof Jack Satsangi</td>
<td>Prof of Gastroenterology, Molecular Medicine Centre, University of Edinburgh</td>
</tr>
<tr>
<td>Dr John Sayer</td>
<td>Honorary Consultant Nephrologist, Newcastle upon Tyne Hospitals</td>
</tr>
<tr>
<td>Dr Claire Shovlin</td>
<td>Reader in Clinical and Molecular Medicine, Imperial College London</td>
</tr>
<tr>
<td>Dr Chantal Simon</td>
<td>General Practitioner &amp; Medical Director for Enterprise and Professional Development, Royal College of General Practitioners</td>
</tr>
</tbody>
</table>

A conversation with clinicians
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Sanjay Sisodiya</td>
<td>Prof of Neurology, Institute of Neurology, UCL</td>
</tr>
<tr>
<td>Dr Ingrid Slade</td>
<td>Specialist Registrar in Public Health, Nuffield Department of Population Health</td>
</tr>
<tr>
<td>Dr Estée Török</td>
<td>Honorary Consultant in Infectious Diseases &amp; Microbiology Cambridge University Hospitals</td>
</tr>
<tr>
<td>Dr Clare Turnbull</td>
<td>Clinical Lead for Cancer, Genomics England</td>
</tr>
<tr>
<td>Dr James Ware</td>
<td>Honorary Consultant Cardiologist, Royal Brompton and Harefield Hospitals</td>
</tr>
<tr>
<td>Dr Alex Whiter</td>
<td>General Practitioner, London</td>
</tr>
<tr>
<td>Simon Wilde</td>
<td>External Affairs Manager, Genomics England</td>
</tr>
</tbody>
</table>
About the PHG Foundation

The PHG Foundation is a pioneering independent think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine. Our mission is to make science work for health. Established in 1997 as the founding UK centre for public health genomics, we are now an acknowledged world leader in the effective and responsible translation and application of genomic technologies for health.

We create robust policy solutions to problems and barriers relating to implementation of science in health services, and provide knowledge, evidence and ideas to stimulate and direct well-informed discussion and debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders. We also provide expert research, analysis, health services planning and consultancy services for governments, health systems, and other non-profit organisations.