

Meeting:	BSGM 100,000 Genome Group
Date:	April 2013
Title:	Delivering the 100,000 Genome Project in the NHS
Report to be considered in public or private?	Public
Purpose - what question does this report seek to answer?	BSGM Strategic Proposal to deliver 100,000 Genome Project
Reference/s:	HGH Genomic Report Jan 2012 Life Sciences Strategy Dec 2011 Life Sciences Strategy One Year On Dec 2012
Resource impact:	£100M
What action is required at this meeting?	Receive and note the content and the recommendations
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The BSGM's Proposal to Support the Delivery of the 100,000 Genome Project in the NHS

1.0 Executive Summary

The British Society for Genetic Medicine (BSGM) represents 2000 clinicians, scientists and academics in the UK. The diversity of the membership reflects the complex integration of multiple disciplines required to deliver genetic medicine to NHS patients. Medical Genetic Services in the UK are upheld as an exemplar of good practice internationally. The diversity of the membership has provided the direction and expertise to convene three meetings on optimising delivery of the 100,000 genomes initiative, on which this report is based.

The BSGM believes that a significant component of the rare diseases element of the Government's 100,000 Genome strategy can be delivered with support from the Regional Genetic Services (RGSs) in collaboration with Pathology services, Academia and Industry. The Genetic community is therefore ideally positioned to provide the leadership that will be needed to ensure the successful outcome of this project. The BSGM therefore proposes a strategy, outlined in this document, as a potential model to support the delivery of this exciting project, sequencing the genomes from NHS patients with rare diseases and cancer, to diagnostic standard.

Results from Whole Genome Sequencing can supplement but not yet replace existing methods due to the uncertainty with respect to depth of coverage of the Genome, inability to deal with large scale copy number variants and the higher error rates. Whole Exome Sequencing (WES), which might be referred to as Functional Genome Sequencing (FGS), is already finding a place in routine diagnostics and some Regional Genetic Services (RGSs) are already offering testing using this new and innovative platform, as it provides the ability to sequence the functional genes across the whole Genome in parallel. The RGSs in the UK also have a track record in setting standards, which will also underpin health applications of these new genomic technologies.

The RGSs, as members of the BSGM, have the ability to come together as a network to provide NHS Governance assurance to the public for safer services and quality of care. To this end, the BSGM make a number of recommendations in this document to facilitate the support of the 100,000 Genome project, including; the establishment of a Strategic Clinical Network for Genetic Medicine under the wing of the new Networks and Senates structure, providing a model of quality assurance and accelerated absorption of 100,000 genome developments into routine care. In addition, further development of the NHS Infrastructures already in place, such as the Diagnostic Mutation Data Base (DMuDB - National Genetics Reference Laboratory Manchester) and DECIPHER database (Cambridge) need to be supported to become more readily usable by the clinic and laboratory. These Databases would function on a national level protected by NHS Information Governance standards and provide the archiving resource for the 100,000 Genome project.

A robust consent and patient information plan is essential and can be piloted via genetic clinics while early recruits are sought to the whole genome sequencing process to test data processing and assess the impact of this new technology on service delivery.

Large scale recruitment of patients referred to the Regional Genetic Services should be a major contribution to the challenge of identifying rare disease patients in whom sequencing can offer improved diagnosis. The capacity of existing genetics staff to handle complex data and process it efficiently using available online resources will be enhanced by the roll out of formal training and development of improved software as a consequence of on-going delivery of this project.

Whole genome sequencing will, through this strategy, become embedded in clinical practice and transform diagnostics such that identification of likely genetic causes will be seen as an introduction to a patient's journey rather than a rare and delayed contribution available to a minority.

Finally, as a measure of success, Genome sequencing with appropriate clinical utility will be embedded in the NHS and delivered as a safe service. This would provide a wider breadth of disease knowledge, without the unaffordable impact on the NHS in the future.

2.0 Purpose of the Document

This document has been prepared by the British Society for Genetic Medicine (BSGM – formerly known as British Society for Human Genetics, BSHG) 100,000 Genome Project Group, and provides professional input and support to the strategic proposal for the delivery of the Life Sciences Strategy (2012) for 100,000 Genomes sequenced to diagnostic quality, in the NHS, for the benefit of patients, to address the health needs of the UK population and stimulate wealth creation by the UK based Bioscience Industry.

3.0 British Society for Genetic Medicine (BSGM)

The British Society for Genetic Medicine (BSGM) represents 2000 clinicians, scientists and academics in the UK. The diversity of the membership reflects the complex integration of multiple disciplines required to deliver genetic medicine to NHS patients. Medical Genetic Services in the UK are upheld as an exemplar of good practice internationally. The BSGM recognises that genomic science will be at the core of biomedical diagnosis and central to the practice of most medical disciplines in this decade. The membership of the BSGM is excited about the opportunities for improving healthcare through genomic sequencing and keen to contribute their expertise to maximise patient benefit.

The patient journey is currently benefited by easy referral routes, through Regional Genetic Services that integrate with primary and secondary care with close integration between clinical and laboratory services, improving diagnostic accuracy and interpretation and furthermore, intimate links with academic partners in translating new knowledge and technology for patient benefit. BSGM members provide end-to-end care along the entire patient pathway from referral, through diagnostic testing, research, and back to informed clinical management.

The outlook of the BSGM is wide, with membership also drawn from mainstream medical specialities including oncology, cardiology and ophthalmology. The recent change of name and internal structure has been driven by a desire to be at the centre of the developments in Genetic Medicine; to this end the BSGM aims to form an umbrella organisation, not only for those with a direct professional interest as the doctors, nurses, counsellors and scientists, within the Regional Genetics Centres, and also the wide and growing spectrum of clinicians across healthcare involved in translating genetic knowledge into improved diagnosis, treatment and prevention.

The BSGM was quick to draw on this diverse expertise to convene three meetings on optimising delivery of the 100,000 genomes initiative, on which this report is based.

The BSGM believes that a significant component of the rare diseases element of the Governments 100,000 Genome strategy can be delivered with support from the regional Genetic Services in collaboration with Pathology services, Academia and Industry. The Genetic community is therefore ideally positioned to provide the leadership that will be needed to ensure the successful outcome of this project.

3.1 Our Shared Purpose

The membership of the BSGM has a shared purpose in supporting the delivery of this project, to facilitate better outcomes in healthcare for Patients, treating the sick, caring for people and through this innovation, ensuring the investment in the NHS results in more effective, efficient and safe services for patients. To this end the BSGM proposes the following:

1. BSGM welcomes and supports the implementation of diagnostic Whole Genome Sequence (WGS) testing in clinically appropriate cases.
2. BSGM welcomes and supports efforts to increase diagnostic sequencing capacity and quality for NHS patient benefit.
3. NHS genetic services will have a critical role because of their wide experience in genetic testing as part of patient diagnosis and care, undertaking this directly and by providing support to other medical disciplines such as cardiology, ophthalmology etc.

4. NHS genetic services are keen to support the development and implementation of new diagnostic sequencing services, particularly in clinical interpretation, confirmation and feedback to patients and relatives.
5. The BSGM recognises that the new programme will need careful planning and implementation to ensure success in providing patient benefit both in the immediate and longer terms. To achieve this requires multi-disciplinary collaboration and inter-disciplinary learning and trust. BSGM can provide leadership across these disciplines.
6. Regional genetics services and BSGM members will promote the importance of contributing and sharing data in order to enhance future capabilities. They are well placed to explain and promote this with patients, the public and other professional colleagues.
7. Regional genetics services and BSGM members have good understanding and experience of current methods of assessment of genetic tests through the 'Gene Dossier' process and the work of the UKGTN. They would be well placed to undertake work to develop this system under the new paradigm.
8. BSGM accepts that more than one provider model for sequencing provision to the NHS may be appropriate.

4.0 Introduction and Background.

Genomics represents a technological advance in the analysis of DNA and related molecules, is applicable to all life forms and has relevance across all aspects of human endeavour. In medicine, genomics embraces the analysis of foodstuffs and pathogens, underpins therapeutic development and will transform diagnostics and the potential for regenerative medicine. Within this broad concept of "Genomic Medicine" lies the application to better understanding of the relationship between the human genome and human disease.

Genetic Medicine: This term can embrace the activities of a wide range of practitioners interested in analysing genetic variation in the germline and somatically, to better understand any disease. An important focus is to identify and provide appropriate care to those with a constitutional change, which causes or predisposes them to a malformation or disease. Many of these disorders are very rare yet impose a massive burden on the individual and their family, who may also be at risk. In other situations the genetic disease is more common yet fails to be recognised, as it is obscured by an even more common disease process. Hereditary forms of breast and colorectal cancer or familial hypercholesterolemia are good examples of diseases where the majority of those at risk go unrecognised and untreated.

The cost of sequencing a human genome has decreased 100,000 fold over the past decade, and over the same period, the time taken to sequence a genome has fallen from ten years to a single day. We will soon be able to sequence a human genome for under £1,000, and the cost is likely to fall further in the coming years. With this ability to interrogate human genomes rapidly and cheaply comes the prospect that many aspects of medicine will be revolutionised.

This Genomic sequencing has the ability to transform patient care from a Genetic perspective, and is evolving rapidly. Despite the falling costs it is undesirable to have individual hospitals and healthcare teams attempting to adapt to the changing technological environment and absorb the major informatics challenge in isolation. This will be inefficient and fail to take advantage of the potential for a large scale integration of genotypes with phenotypes. On the other hand, this unique and ambitious programme will not be judged a success if the regional capacity for delivery of genetic and genomic medicine is not developed in parallel.

The BSGM therefore proposes the following strategy, as a potential model, to support the delivery of this exciting project, sequencing the genomes from NHS patients with rare diseases, to diagnostic standard.

5.0 Learning from Good Practice

Delivering innovation at scale and pace is common place in Genetics and there are many areas of good practice to learn from both in the UK and abroad. Learning from what has gone before has helped to shape this strategy and create a common approach; we can look to projects such as Deciphering Developmental Disorders (DDD) and Evaluating ArrayCGH in Prenatal Diagnosis of Fetal Anomalies (EACH). Through projects like these, UK researchers have very successfully utilised whole genome analysis to identify novel disease genes and new disease mechanisms. The majority of these researchers are active clinicians based in Regional Genetic Centres. Regional genetics laboratories have worked with their research colleagues to translate these technological developments into improved diagnostic tests and a portfolio of “panel tests” (where 2-105 genes are simultaneously analysed in a single test) is now being commissioned. There has also been interaction with colleagues abroad, to share experiences and learning (e.g. Baylor College, Texas, USA; Radboud University, Nijmegen, the Netherlands; FORGE project, Canada).

Results from Whole Genome Sequencing can supplement but not yet replace existing methods due to the uncertainty with respect to depth of coverage, inability to deal with large scale copy number variants and the higher error rates.

Whole Exome Sequencing (WES), which might be referred to as Functional Genome Sequencing (FGS), for this purpose, is already finding a place in routine diagnostics and some RGSs.

In the area of Cancer, the Stand Up to Cancer (SU2C) project will sequence 600 cancer genomes from castrate resistant prostate cancer biopsies to identify genetic variants for administering targeted therapy. Initially this will involve exome sequencing and progress to whole genome analysis. This project is already underway and includes individuals from the UK in this initiative (Profs de Bono and Eeles, The Institute of Cancer Research, Sutton, UK). Expertise from this group, as members of the BSGM 100,000 Genome Group, will provide learning and good practice to this project to ensure greater success.

6.0 Creating New Standards; Influencing International Practice

The RGSs in the UK have a track record in setting standards, which will also underpin health applications of genomic technologies. Existing national standards include; CPA/UKAS laboratory accreditation aligned to ISO15189, the UK National External Quality Assessment Schemes, the quality requirements for UKGTN membership and the consent and confidentiality guidance from the Joint Committee on Medical Genetics. These achievements have significantly influenced international standard setting.

Examples of such standards of practice are the 2008 protocol on genetic testing of the Council of Europe <https://wcd.coe.int/ViewDoc.jsp?id=1354789> and the recommendations adopted by the Organisation for Economic Co-operation and Development for Quality Assurance in Clinical Molecular Genetic testing (2007) www.oecd.org/science/biotechnology/policies/38839788.pdf.

In addition, major international Laboratory Proficiency Testing networks (European Molecular Genetics Quality Network and Cytogenetics European Quality Assessment) are headquartered in the UK linking over 1,100 laboratories in more than 60 countries world-wide; EMQN and UKNEQAS are jointly piloting a quality assessment scheme for next generation sequencing with results expected this year.

A high profile output from the 100k project should be national standards to inform the development of international 'Good Genomic Practice.' This should be aligned with ISO norms to sit alongside respectively Good Laboratory, Clinical and Manufacturing Practice. We recommend that the UK government raise this as a potential work-stream with the relevant international bodies, including the Science and Technology Directorate of the OECD.

Recommendation 1: The BSGM will work with the DH and others to develop national standards for whole genome sequencing with a view to informing international practice.

7.0 The Role of UKGTN Data Sharing and Compliance

The United Kingdom Genetic testing Network (UKGTN) continues to evolve. The model of patient DNA samples moving between centres for disease/gene specific tests is already less relevant as generic (panel/exome/WGS) analyses are adopted by most centres, designed to answer clinical questions framed by a broad set of symptoms (cardiac/renal/neurological/metabolic). In this situation, it may be that information rather than clinical samples becomes a network currency. The gene dossier test assessment system requires development to fit this new paradigm. New network drivers are required; particularly an obligation to contribute and share data to the 'National Genomic Intelligence Network' proposed to link to the 100k project and other repositories. Data sharing has already been included as a requirement in the new Medical Genetics Specialised Service specification; a specific CQUIN for NHS services and a contractual requirement for private sector providers could be key incentives for compliance.

Recommendation 2: The BSGM will work in collaboration with UKGTN to promote the established precedents of high quality testing with clinical utility and equity of access for genomic tests commissioned through the national commissioning boards.

Recommendation 3: The BSGM will support the Medical Genetics Clinical Reference Group to help design incentives and key performance indicators, to promote data sharing amongst all genomic test providers.

8.0 Building on Existing NHS Structures

8.1 Role of a Strategic Clinical Network

Clinical networks are an NHS success story. Combining the experience of clinical teams, the input of patients and the organisational vision of NHS staff, they have supported and improved the way we deliver care to patients in distinct areas e.g. Cancer Networks. Strategic Clinical Networks linking primary, secondary and tertiary care will be able to ensure safe, effective and efficient services. A Strategic Clinical Network for Genetic Medicine would encourage standardisation and adoption of best practice across the UK, leading to measurable improvements in both outcomes and experience for patients. Such a Network will have the ability to raise standards and support easier and faster access to services.

The Regional Genetic Services (RGSs), as members of the BSGM have the ability to come together as a network to provide NHS Governance assurance to public for safer services and quality of care. Genetic Services are a partnership of medically qualified clinical geneticists, registered genetic counsellors and clinical genetic scientists providing a systematic care pathway for patients, bringing the science to the clinicians and linking phenotype to genotype. Representatives of the RGSs would link with the broader clinical community involved in genetic medicine and patient support groups to provide long term horizon scanning, improve services and help strategically plan pathway models of care. A Strategic Network would provide leadership and education for mainstreaming Genetic testing and standardised Genomic testing available to all medical specialities fulfilling the expectations articulated by consecutive Governments in the Publication of the 2003 White paper 'Our Inheritance our future' and more recently in the Genomic Review (2012) 'Building on our inheritance, Genomic Technology in Healthcare'.



Building on our inheritance _ A report

The reorganisation of specialist commissioning offers the opportunity to create an operational delivery Network alongside a Strategic Clinical Network for Genetic Medicine which would allow centralised procurement of technologies and widespread adoption through set standards monitored by the Network. It could provide a central bioinformatics resource and repository for accurate clinical interpretation, and oversee the development of bioinformatics systems in collaboration with Academia and Industry to provide

more accurate interpretation of deep sequence based analysis to Diagnostic Quality. An operational Network would also be in a position to standardise procedures and systems, curate data, ensure governance and provide assurance on the appropriate availability of data for research.

This Network would ensure a nimble flexible model of assurance, adaptable to changing technology and environment and fit a changing landscape while still being functional in 5 years' time. Such a Network will underpin the success of the Genomic revolution for the benefit of patients across the NHS and would reflect the successful model of a Genetic Consortium, already in existence in Scotland, which would have representation on this NHS Network along with representatives from other devolved countries.

Recommendation 4: The BSGM propose the establishment of a Strategic Clinical Network for Genetic Medicine under the wing of the new Networks and Senates structure. In management of the routine care of people with rare genetic diseases, the option of an Operational Network of Regional Genetic Services under the supervision of the Specialty Commissioning Authority is worthy of examination. This can offer planning of the comprehensive Services, both patient facing and laboratory testing, providing a model of quality assurance of Genetic Services and accelerate absorption whole genome sequencing into routine care.

8.2 Developing Existing Databases

NHS Infrastructures already in place, which can be further developed include: the Diagnostic Mutation Data Base (DMuDB - National Genetics Reference Laboratory, Manchester) and the DECIPHER database (Cambridge). From spring 2013, the DECIPHER database (<http://decipher.sanger.ac.uk>) will integrate sequence and structural variants, enabling the full spectrum of genomic variation to be interpreted within a secure, web-based system incorporating a genome browser designed for clinical use. A custom recruitment and reporting module has been created within DECIPHER for the Deciphering Developmental Disorders project (www.ddduk.org). More than 13,000 samples have been registered in the system to date. The DDD module contains a 'drag and drop' phenotyping tool utilising the Human Phenotype Ontology (HPO), together with a patient information form and a panel of known developmental disorder genes (DDG2P). This system has been custom designed and coded within DDD-DECIPHER for rare childhood genetic disorders.

With the appropriate resource, this modular system has the potential to be expanded rapidly to support the genomic analysis of patients with all forms of rare genetic diseases.

Recommendation 5: Further development of the NHS Infrastructures already in place, the Diagnostic Mutation Data Base (DMuDB - National Genetics Reference Laboratory Manchester) and DECIPHER database (Cambridge) need to be supported to become more readily usable by the clinic and laboratory. These Databases would function on a national level protected by NHS Information Governance standards.

One of the main outcomes of the 100,000 genomes project will be the ability to aggregate rich genotype and phenotype data, which has uniquely passed through the accredited processes of diagnostic laboratories and therefore represents data of the highest quality. This is vital for the interpretation of variants as they are detected. Although NGS platforms will generate many thousands of variant calls for each patient, the final report issued to a referring clinician, representing the interpreted variant or variants of clinical significance to the patient, will be reported to the same diagnostic standard as those from conventional testing. Such variant information has been carefully collected and shared in the DECIPHER and DMuDB projects, it is vital that data already aggregated, and the expertise and networks developed by these projects, are incorporated into the central data control, which will form the heart of the 100,000 genomes project, and that this takes place within the NHS framework.

Consistent with this aim the DH has long-listed an informatic project under its High Impact Innovation Initiative. This was discussed at the HGSG and by the Clinical Reference Group. The 'Genomic Clinical Workbench (GCW) is designed to link existing informatics tools forming the life cycle of a genetic investigation from patient phenotype and test request to capture of analytical results for repositories and the electronic patient record.

Recommendation 6: Resources to develop Genomic Clinical Workbench should form a proposal to the Specialised Services Commissioning Innovation Fund.

9.0 The Strategic Vision

9.1 The Science – Defining the Genomes

There are over 7000 rare disorders with a genetic basis that collectively affect 6% of the UK population. Many are chronic diseases associated with substantial morbidity and premature mortality. The genetic cause is known for only half of these, but genomic sequencing is identifying up to 30 novel disease genes each month. A genetic diagnosis provides a definitive diagnosis, allows accurate genetic counselling and may lead to improved treatment.

Genomic sequencing offers the potential to sequence almost all of the 21,000 genes simultaneously to identify mutations in any known gene or discover new aetiologies. There are, however, formidable logistical and ethical challenges for the implementation of genome sequencing as a diagnostic test. The ability to confidently identify a pathogenic mutation from the >1 million variants per genome is essential. Increased knowledge of “normal” variation is necessary but in the short-term analysis might initially be restricted to known genes linked to the patient phenotype. The depth of coverage necessary to achieve “diagnostic quality” is not clear and research is needed to estimate false negative and false positive rates according to genome coverage. Genome sequencing has the potential to replace almost all types of genetic test (Sanger sequencing, CNV analysis by aCGH or MLPA, and karyotyping to detect balanced rearrangements) once validated for diagnostic services and assuming that it proves cost-effective in health economic assessments.

The priority for the rare disease part of the 100,000 genome project will be identifying patients with a high likelihood of a genetic disease and for whom a genetic diagnosis will bring clinical benefit. These may be patients for whom existing tests or participation in research studies has failed to achieve a diagnosis and/or those likely to have de novo mutations or where parental consanguinity will limit the number of candidate variants. Confirmatory sequencing in an accredited laboratory, segregation testing and genotype/phenotype analysis will be required before genome sequencing results can be reported. Data sharing of novel variants linked to phenotypic data will enhance the interpretation of current and new NHS diagnostic tests.

9.2 Bioinformatics – Data storage and Handling

Development of new bioinformatic systems and standards will be essential to the success of the 100,000 genomes project. The RGSs have engaged in the development of standards relevant to the handling and exchange of data over many years, including; the ‘Do Once and Share’ project, the specification of the STARLIMS laboratory management system, the National Laboratory Medicine Catalogue and development of draft NHS standards for genetics by UKGTN in 2012. Furthermore, the adoption of common laboratory platforms like STARLIMS and, to a lesser extent, clinical genetic patient management systems, has provided the foundations to develop the network interfaces that will be necessary to engage with the 100,000 genomes project. The Regional Genetic laboratories are also engaged in developing data storage and handling procedures and systems within their own Trusts, to meet the challenges of NGS technologies, and have developed knowledge and expertise in this area. A Strategic Clinical Network for Genetics therefore will be well placed to rapidly understand and meet the bioinformatic challenges of the 100,000 genomes project and to provide effective collaboration to achieve its success.

9.3 Clinical Delivery, Ethics and Patient Engagement – The Patient Perspective

Members of the BSGM are very much involved in all aspects of the patient journey through the Genetic Pathways. This is facilitated by easy referral routes, through regional services that integrate with primary and secondary care; close integration between clinical and laboratory services, improving diagnostic accuracy and interpretation; intimate links with academic partners in translating new knowledge and technology for patient benefit. BSGM members provide end-to-end care along the entire patient pathway from referral, through diagnostic testing, research, and back to informed clinical management

The membership of the BSGM aspire to be involved with the choice of patients for testing (either those attending clinical genetics services or rare disease services elsewhere including inherited cardiovascular disease and inherited metabolic disease services). To be concerned with issues of consent and particularly providing information about what patients may or may not know regarding the clinical question, extra information learned from WGS (incidental health related findings) and what will happen to the data. The knowledge, experience and skills of the Genetics Team provide the ideal environment to communicate results to patients (both related to clinical questions and extra information) and provide advice and follow-up for patients and families, assess the outcomes for individual patients of the testing in terms of diagnoses made, changes in health, reproductive choice or uptake of preventive options for patient or family and streamlining of the care pathway. All of which is part of the role the profession has undertaken for decades.

There are a few principles that must run through all steps taken to secure public engagement and, hopefully, endorsement for this programme. These are:-

Transparency: Subject to the need to preserve patient and family confidentiality and, if and when appropriate, commercial confidentiality, the default position should be that information about the project is publicly available – and in a form that is accessible to non-technical people as far as possible. The case for confidentiality needs to be made if it is felt that harm may result from disclosure and not vice versa.

Clarity: Between Research and Clinical Practice, while the boundaries between the two are not always easily drawn in genetics/genomics, and there often seems to be a continuum that extends from clinical practice through detective work and on into research, it is important that this uncertainty is acknowledged in order to establish and sustain a realistic understanding of potential benefits and possible risks associated with this programme. (This is separate from the consent issues affecting potential sample donors).

Scrutiny: Ensuring appropriate scrutiny of the use of data by an appropriate body.

The BSGM also welcomes the invitation from Prof. Sir Mike Richards (NHS CB) to participate in the Clinical and Patient Consultation Workshop, considering the entire process from consent, sample collection and processing, to discussion of results, which is to take place 26th April 2013, and is happy to share this report with that group prior to the meeting.

10.0 Proposed Model for delivering 100,000 Genomes

The BSGM proposes to support the production of a progressive plan, sensitive to patient needs and well detailed with evidence base that will support the delivery of the 'Rare Disease' arm of the 100,000 Genome project.

Existing projects in the translational research portfolio such as DDD, EACH and the CRUK Stratified Medicine projects already comply with the NHS research governance and ethics processes and provide a tested framework which could be used to develop the rare disease arm of the 100,000 Genome project as a translational research endeavour. All suitable undiagnosed patients referred into RGSs could be offered recruitment into the project. Every patient could then have conventional testing and successively exome followed by whole genome sequencing. Bioinformatics for interpretation could then inform the development of a network standard. Evidence from the DDD project indicates that patients are happy and willing to enter into a research project under this model. The 100,000 Genome project will result in 'tooling up' NHS RGSs to provide more effective and efficient service delivery in the future.

In the past 5 years RGSs have successfully implemented Microarray technology, providing Whole Genome analysis for Copy number variants (gains or losses of Genetic material, at a resolution of 50KB, with abnormalities as small as 10kb being resolved). Up to 25,000 cases per annum are now routinely tested and analysed using array technology in the UK, for which incidental findings are the norm. The UK profession has built on the guidance published in the American Clinical Genetics journal, ACMG, in 2012, which provided common practice in this area. This common practice has been ratified by ISCA and the ACC, and these principles will be followed and built on in the interpretation of whole genome analysis using Exomes and Next generation sequencing for whole Genomes. This could provide clinicians with access to

genotype information that when brought together with the phenotype information would enable more appropriate test panels to be developed and utilised in the future.

A key element in this process is development of a manageable policy for reporting incidental findings. Decisions are needed on the probability that particular variants are truly pathogenic, the probability that they will actually cause disease in this context rather than when associated with a classic phenotype, and the availability of meaningful intervention. In order to avoid burdening people with information of uncertain significance, it is necessary to have a “curtain” between those analysing the data and the clinician seeing the patient. The team in Nijmegen (Netherlands) have demonstrated the effectiveness of this approach in their early deployment of Exome capture in children with unknown syndromes.

10.1 Alignment with International Initiatives

Genomic research is expanding on a global scale and there is a clear need to keep abreast of relevant international initiatives that the UK 100,000 Genomes Project should connect with. The research impact of the datasets produced under 100,000 Genomes will be greatly potentiated if they are able to be pooled with data produced in other projects internationally. Such data sharing is in the best interests of patients as it increases the likelihood of diagnostics and therapy development relevant to their conditions. However, it raises a number of strategic questions, such as the need for patient consents to include the possibility of data sharing, the need to align with international policies and standards, and the need to establish mechanisms to ensure all data producers deposit the generated data in appropriate open or controlled access databases. Existing UK initiatives such as the DDD study are based on a similar premise and would form a strong foundation for this approach.

The benefits of data sharing are particularly evident in the rare disease field, where the scarcity of patients and the high phenotypic heterogeneity of the diseases, combined with the lack of knowledge, information and training, still results in frequent delays in diagnosis or in many cases the absence of genetic diagnosis. The International Rare Diseases Research Consortium (IRDIRC, www.irdirc.org), a global grouping of funders including UK bodies such as the NIHR, has set a goal of diagnosing all rare diseases and developing 200 new rare disease therapies by the year 2020. The policy documents currently being ratified by the IRDiRC cite data sharing, including deposition of raw data in open or controlled access databases, as a key policy guideline. One of the flagship projects funded by the European Union under the IRDiRC, the UK-led RD-Connect project (www.rd-connect.eu), is developing a centralised platform for rare disease ‘omics’ data. Under the RD-Connect plans, raw data from multiple rare disease omics projects is deposited with the European Genome-Phenome Archive (EGA) and then run through a single standardised pipeline, with the resulting processed data being accessible to approved researchers in the RD-Connect data coordination centre. With appropriate mechanisms in place, rare disease genomes sequenced under the 100,000 Genomes project could also be considered for inclusion in this initiative.

A further consideration should be that the databases/registries, wherein the clinical data relevant to the patients whose genomes are sequenced are stored, should also be interoperable with current and future international initiatives, such as the platforms planned within RD Connect and the registries platform planned at the Joint Research Centre. Therefore, careful consideration should be given to accurate and consistent coding and the use of agreed common data elements.

Recommendation 7: Patient consent for whole genome sequencing should include explicit consent for sharing of genomic and clinical data.

Recommendation 8: Consideration should be given to the possibility of developing an overarching policy for deposition of all generated datasets in appropriate open or controlled access databases, including the DECIPHER database and European Genome-Phenome Archive (EGA).

10.2 What we will deliver in short term (3 - 12 months)?

A robust consent and patient information plan is essential and can be piloted via genetic clinics while early recruits are sought to the whole genome sequencing process to test data processing and assess the impact on service delivery.

10.3 What we will deliver in medium term (12 - 36 months)?

Large scale recruitment of patients referred to the Regional Genetic Services should be a major contribution to the challenge of identifying rare disease patients in whom sequencing can offer improved diagnosis. The capacity of existing genetics staff to handle complex data and process it efficiently using available online resources will be enhanced by the roll out of formal training and development of improved software.

10.4 What we will deliver in long term (36 - 60 months)?

Whole genome sequencing will become embedded in clinical practice and transform diagnostics such that identification of likely genetic causes will be seen as an introduction to a patient's journey rather than a rare and delayed contribution available to a minority.

10.5 How could we measure success?

A measure of success would be Genome sequencing with appropriate clinical utility, embedded in the NHS and delivered as a safe service. This would provide a wider breadth of disease knowledge, without an unaffordable impact on the NHS.

Evaluation and what is achieved clinically could be measured by a series of audits, undertaken by individuals already available to the profession; Trainee Scientists (Scientist Training Programme - MSC), Trainee Genetic Counsellors and Trainee Clinical Geneticists (Specialist Registrars). These audits could be part of their respective training programmes and also providing evidence of learning outcomes and through these audits also present opportunities for multiprofessional working. These evaluations could be more than just supporting the delivery of the project; they could involve patient and public surveys and measures of improvement in population outcomes, in addition, evaluating the cost to the system and whole health economy. The use of local trainees would also provide opportunities for local projects that might arise as a consequence of the 100,000 Genomes project, to be undertaken, underpinning the R&D and Innovation element of learning outcomes for individuals.

Families affected by hereditary forms of colorectal and breast/ovarian cancer and people with familial hypercholesterolemia are examples of "common rare diseases" amenable to effective, even curative, intervention yet usually missed by our standard methods of diagnosis. The genomic revolution offers an opportunity to make the diagnosis either when people present with a relevant pathology such as ovarian cancer or even when undergoing routine health checks. For example, a recent study shows that cholesterol measurement in toddlers when they receive their inoculation is deemed acceptable to parents and identifies a large majority of children who will benefit from early statin introduction while also allowing cascade testing of adult relatives. Such approaches are challenging because they are in conflict with the model of healthcare delivery developed over generations in Genetic Services, yet from a public health perspective they greatly increase the number of people who can be helped by what are now highly effective preventive therapies. It will be necessary to maintain an open mind in designing evaluation of such approaches and ensure a holistic approach to the measurement of costs and benefits.

11.0 Conclusions

The NHS CB will procure the sequencing, storage and bioinformatics capacity and it is likely that commercial providers will be part of the provision. It has also been stated many times that the Project is first and foremost for **clinical use** and, therefore, the sequencing must be used to provide diagnostic benefit for patients. The BSGM believes this is where the Regional Genetics departments can be of great utility to maximise patient benefit and reduce risk. The role of the BSGM members and Regional Genetics services could be to work with the on-going Project to:

1. Make proposals about the clinical interface with the project
2. Be involved with the choice of patients for testing (either those attending clinical genetics services or rare disease services elsewhere, such as inherited cardiovascular disease or inherited metabolic disease services)

3. Be concerned with issues of consent and particularly providing information about what patients may or may not learn regarding the clinical question, extra information learned from WGS and what will happen to the data
4. Set standards for the required testing (Regional Genetics departments have good understanding of existing standards and a track record in setting standards)
5. Receive sequence variant call files for confirmation of likely pathogenic mutations, co-segregation studies and interpretation of these results in the context of the patient phenotype
6. Communicate results to patients (both related to the clinical question and extra information) and provide advice and follow-up for patients and families
7. Assess the outcomes for individual patients of the testing in terms of diagnostic rates, changes in health, reproductive choice or uptake of preventive options for patient or family and streamlining of the care pathway
8. Assess the implications (both positive and negative) for specialised genetics services and wider health services
9. Be involved in a wider evaluation of the Project as a whole

12.0 Recommendations

Recommendation 1: The BSGM will work with the DH and others to develop national standards for whole genome sequencing with a view to informing international practice.

Recommendation 2: The BSGM will work in collaboration with UKGTN to promote the established precedents of high quality testing with clinical utility and equity of access for genomic tests commissioned through the national commissioning boards.

Recommendation 3: The BSGM will support the Medical Genetics Clinical Reference Group to help design incentives and key performance indicators, to promote data sharing amongst all genomic test providers.

Recommendation 4: The BSGM propose the establishment of a Strategic Clinical Network for Genetic Medicine under the wing of the new Networks and Senates structure. In management of the routine care of people with rare genetic diseases, the option of an Operational Network of regional Genetic Services under the supervision of the Specialty Commissioning Authority is worthy of examination. This can offer planning of the comprehensive Services, both patient facing and laboratory testing, providing a model of quality assurance of Genetic Services and accelerate absorption of whole genome sequencing into routine care.

Recommendation 5: Further development of the NHS Infrastructures already in place, the Diagnostic Mutation Data Base (DMuDB - National Genetics Reference Laboratory Manchester) and DeCIPHER database (Cambridge) need to be supported to become more readily usable by the clinic and laboratory. These Databases would function on a National level protected by NHS information governance standards.

Recommendation 6: Resources to develop Genomic Clinical Workbench should form a proposal to the Specialised Services Commissioning Innovation Fund (SSCIF).

Recommendation 7: Patient consent for whole genome sequencing should include explicit consent for sharing of genomic and clinical data.

Recommendation 8: Consideration should be given to the possibility of developing an overarching policy for deposition of all generated datasets in appropriate open or controlled access databases, including the DECIPHER database and European Genome-Phenome Archive (EGA).

Appendix 1

Membership of BSGM 100,000 Genome Group

John Burn	Chair, BSGM, NHS CB 100,000 Genomes Strategy Group
Angela Douglas	Deputy Chair BSGM, Chair, ACGS, Chair, ACC
Hilary Burton	Rare Diseases Subgroup (Genomic Strategy Group)
Christine Patch	Rare Diseases Subgroup (Genomic Strategy Group)
Helen Firth	Science Group (Genomic Strategy Group), DDD Project
Graeme Black	Regional Genetics Service, MCH and Manchester University
Sian Ellard	Science Group (Genomic Strategy Group), CRG
Rob Elles	CRG
Adam Shaw	General Secretary, BSGM & Joint Lead for Cancer Genetics, King's Health Partners
Phil Beales	GOS, UCL Rare Diseases
Alistair Kent	Genetic Alliance UK
Nick Meade	Genetic Alliance UK
Frances Flinter	CRG, new group to advise Mike Richards – Clinical Engagement
David Baty	Chair, CMGS
David Bonthron	
Rosalind Eeles	Institute Cancer Research, London
Andrew Devereau	NGRL, Manchester
Anneke Lucassen	Southampton, CMO 100,000 Genomes WP-ethics.
Kate Bushby	Newcastle University
Hanns Lochmuller	Newcastle University