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NHS National Services Scotland

Genomics for Rare Disease in NHS Scotland

The bridge to a Scottish Strategy for Genomics: Report 1 (June 2019)

Contents

Executive Summary

Genetic and genomic testing occupy a vital role within Precision Medicine, which is about offering the right treatment at the right time based on an individual's molecular and genetic characteristics. Scottish physicians and scientists have made world-leading contributions to research on rare disease genetics and genomics; and a well-established network of clinicians and clinical scientists have been delivering evidence-based genetic testing for NHS Scotland (NHSS) patients for over thirty years.

NHSS's National Services Division (NSD) is responsible for commissioning and performance managing national Specialist Services, including laboratory genetics services, across Scotland. The laboratory genetics service for Scotland is provided via a Scottish Genetic Laboratory Consortium (SGLC) of four regional genetics centres in Aberdeen, Dundee, Edinburgh and Glasgow. Through the consortium approach, the four centres work together to avoid duplication, and to provide genetic testing for a wide range of conditions efficiently and equitably across the entire geography of Scotland.

Laboratory genetics is an evolving field, with the workload increasing by as much as 10% each year as advances in technology and knowledge increase the range of conditions which can be tested. Scottish Government has included a commitment in the Programme for Government 2018/19 to continue the development of genomic medicine through the enhancement of NHSS genetic capabilities for the diagnosis of rare diseases. This will build on current practice and experience gained in genomic technologies; including ongoing collaboration between the SGLC and NSD with the Scottish Genome Partnership (SGP), as well as improved data analysis, sharing and storage.

SGP is a major Scotland-wide research programme between the Universities of Edinburgh, Glasgow, Aberdeen and Dundee, with NSD and SGLC. It was funded by the Scottish Government's Chief Scientist Office and the UK's Medical Research Council to undertake research on the use of genome sequencing for medical benefit. Research by SGP included a collaboration with Genomics England on the 100,000 Genomes Project, which aimed to sequence 100,000 genomes from UK families, including those affected by rare conditions, in order to provide a diagnosis for some patients with rare diseases and develop future NHS healthcare services. As a result of the 100,000 Genomes Project, from late 2019, genome testing will become routinely available to some NHS England patients for a limited range of conditions; however, the evidence to support the benefits of these tests in the context of a nationalised health service has yet to be described.

The recent allocation of £4.2 million to NSD, SGLC and SGP in the Programme for Government 2018/19 will support the continued development of genome-scale testing for inherited and rare disease in Scotland and act as a bridge until there is sufficient evidence to inform a strategy for the implementation of routine genomic testing for NHS Scotland patients. A stepwise approach has been compiled by NSD working with clinical and scientific leads upon the request of Scottish Government. This approach implements several linked initiatives within SGLC, which will be evaluated for future implementation of genomic testing into mainstream medicine for Scotland. Progress with implementation and the outcomes from this will be regularly evaluated to inform further strategic planning and ensure cost-effective delivery of the most appropriate testing methodology within routine service for optimum patient care. This first 6-monthly report captures key achievements to date, and identifies timelines for future evaluation of the approaches implemented.

Key points to note at this stage:

- Two of the four genetics laboratories had implemented a clinical exome service by 1st April 2019, with the other two due to start imminently. It will be vital that the consortium continuously monitor the clinical exome workload and all other workloads to ensure that the laboratories continue to have the capacity to deliver testing.
- NHS Lothian now expects to commence trio whole exome sequencing and analysis in July 2019, once the requisite procurement and information governance processes are completed.
- The evidence base on which to assess the utility of whole genome sequence tests has started to accumulate as we approach the end of the first phase of funding for SGP ("SGP1" – the first 1,000 genomes). All processes developed for SGP1 will continue to be used as we extend into the second phase of work within the bridge funding ("SGP2"), which includes sequencing and analysis of a further 500 whole genome sequences. This work is subject to complex multi-organisational

agreements and regulatory approvals, all of which are in the process of being updated prior to re-commencing recruitment.

- Adequate data storage and informatics support for clinical care facilitated by a cross-board system for electronic test requesting, sample sharing and result reporting are of the utmost importance for the realisation of Precision Medicine for patient care in NHSS. The SGLC and NSD have recognised this and are currently engaging with NES colleagues who are tasked to implement key elements of the 2018 Digital Health & Care Strategy; discussing potential collaboration around the National Digital Platform (NDP) and Genomics in order to contribute to the delivery of genetic laboratory services for the future.

It is anticipated that the experience and evidence gained throughout the two year bridge funding period will lead to the development of a future testing strategy for rare disease genomic medicine within NHSS, to be implemented following on from the bridge funding.

Background

In July 2017 the *Annual Report of the Chief Medical Officer (2016): Generation Genome* was published, based upon the recommendations set out in this report NHS England (NHSE) embarked an extensive reconfiguration programme of the Genetic Laboratory service provision in England, with the aim of providing a high quality, equitable and cost effective services across the pipeline from sample acquisition, to data analysis, validation and clinical interpretation, with support for patients and families. The specification for the reconfiguration of the NHSE Genetic Laboratory service focused on the genomic laboratory services falling within the direct commissioning responsibilities of NHSE. The issuance of the English National Genomic Test Directory and ongoing integration of the National Genomics Informatics System (NGIS), demonstrated the clear intention for this service to be entirely self sufficient.

There was little to no engagement between NHSE and the other devolved nations at the consultation and planning stages of the reconfiguration of NHS Scotland (NHS) genomic laboratory service provision in England, leading to a great deal of uncertainty regarding future ways of working amongst genetic laboratory centres and cross border relations.

However, this lack of a collaborative approach has since been addressed and the Devolved Nations Working Group (DNWG) was established in November 2017. The group brings together representatives from each of the four nations to ensure that the valuable work and relationships that have been built with colleagues across England, Northern Ireland, Scotland and Wales are retained. Service commissioners NSD and SGLC clinical and scientific leads continue to engage in this collaborative discourse with a view to ensuring that there is a cohesive approach to genomic medicine across the UK.

Circumstances at the time were further compounded by the combination of coinciding events developments;

- *Recruitment to the 100,000 Genomes Project in Scotland, through the Scottish Genome Partnership (and the rest of the UK) had concluded.*

  When the SGP was established one of the aims was to provide evidence to inform the future delivery of NHSS genetics services and to ensure that the learning from genome-based science can be applied within NHS clinical services in Scotland. Recruitment of the initial 1000 Scottish participants was completed in October 2018, and clinical results from Whole Genome Sequencing (WGS) analysis are currently being returned to NHSS genetics laboratory centres for validation and reporting. This will continue over the next 3 months.

  SGP Health Economics analysis to evaluate WGS has begun. Subject to the outcome of a separate funding application to CSO, this analysis will assess the costs and benefits of WGS for the diagnosis of rare disorders, in comparison to other potential health care interventions. The evaluation will form the basis of recommendations about the use of WGS within the Scottish NHS.

- *The Scottish Government had commissioned an inquiry on the development and implementation of Genomic Medicine in Scotland by the Scottish Science Advisory Council.*

  The report entitled '*Informing the Future of Genomic Medicine in Scotland*', has since been published (Feb 2019) and provides an overview of current Genomic Medicine capabilities in Scotland, contrasts these with developments elsewhere in the UK and internationally, and summarises opportunities and benefits for the NHS, research and life sciences sector in Scotland. The report made six broad recommendations;

  1. *Leadership* - Scottish Government should convene a Scotland-wide Genomic Leadership Group (GLG) to advise how best to support the development of Genomic Medicine in Scotland.
  2. *Clinical Implementation* - Scottish Government should support NHSS to expedite evaluation and adoption of genomic testing where there is good evidence of improved patient outcomes.
  3. *Workforce* - NHSS working with NES, ScotGen, Skills Development and academic institutions should lead in co-ordinating the development and delivery of the training courses and

educational resources required to develop essential expertise and drive Genomic Medicine capabilities.

4. *Digital Health* - Scottish Government should take account of the digital infrastructure needed to enable genomics within clinical pathways and to support the use of genomic data.
5. *Research and Innovation* - Scottish Government, working with research funders, industry, enterprise agencies and higher education providers, should consider how best to support genomic research and innovation.
6. *Industry-Facing Activity* - Scottish Government, working with enterprise agencies, should build on the strengths of Scotland's 'triple helix partnership' between academia, the NHS and industry to accelerate genomics development as an integral part of Precision Medicine.

Scottish Government colleagues are actively convening the Scotland Genomic Leadership Group (GLG) to drive forward progress on the other recommendations.

It was against this backdrop of a rapidly evolving clinical / scientific and policy landscape and upon the request of Scottish Government colleagues that NSD, working with clinical and scientific leads, compiled a stepwise strategy, linking several initiatives for the implementation of genomic testing into mainstream medicine for Scotland. The intention of the strategy is to provide a bridge until a long term Scottish Strategy for Genomics is in place.

NHS Scotland Genetic Services: Developing genomics as a cornerstone of clinical care

NHS Scotland genetics services are delivered through four regional genetics centres in Aberdeen, Dundee, Edinburgh and Glasgow. Each centre offers a closely integrated laboratory and clinical service. NHS National Services Scotland (NSS), National Services Division (NSD) commission the four genetics laboratories in Scotland who work as a formal consortium arrangement, the Scottish Genetics Laboratory Consortium, to deliver equitable, high quality genetic testing service for Scotland.

The Consortium structure has provided a forum for clinicians, scientists and commissioners to identify, evaluate and implement the most clinically and cost effective approach to genetic testing consistently across Scotland, taking advantage of national expertise, by developing clinical management pathways that serve across specialties.

The four centres across Scotland, working with four Scottish universities and Genomics England (Scottish Genomes Project; SGP) are evaluating the clinical utility of whole genome sequencing for NHSS patients and their families by contributing 1000 genomes to the 100,000 Genomes Project, funded by the Medical Research Council (MRC) and the Chief Scientist Office (CSO), with experienced staff time contributed by NHSS. The clinical practice and laboratory processes developed in the course of the project are paving the way for exome and genome testing to become standard care in NHSS.

Scottish Government included a commitment in the Programme for Government 2018/19 to continue the development of genomic medicine through the enhancement of NHS Scotland genetic capabilities for the diagnosis of rare diseases. This will build on current practice and experience gained in genomic technologies; including ongoing collaboration between the SGLC and NSD with the SGP as well as improved data analysis, sharing and storage. The recent allocation of £4.2 million will support the continued momentum of genomic work for inherited and rare disease in Scotland and act as a bridge until there is sufficient evidence to inform strategy for the implementation of genomic testing in Scotland.

The SGLC has advocated that the laboratories deliver a mixed portfolio of genetic and genomic tests thereby providing the most clinically useful and cost-effective testing service to inform patient care and management. The bridge funding made available by Scottish Government will allow time for the assessment of these applications of genomics testing in an NHSS setting in the anticipation that the accumulation of data, gathered by the Consortium laboratories, the SGP / 100,000 Genomes Project and progress of the recommendations from the SSAC Report will clearly provide evidence for the value of genomic testing for Scottish patients.

Workstreams & Reporting Cycle

The action plan for the stepwise strategy that is being adopted for the implementation of the bridge to a Scottish Strategy for Genomics sets out that progress will be tracked and the achievement of key milestones captured in regular 6 monthly reports, ensuring that progress is regularly evaluated to inform further strategic planning and ensure cost-effective delivery of the most appropriate testing methodology within routine service for optimum patient care.

Each of the work streams has been attributed tasks to be undertaken and completed to an associated timeline to ensure timely progress and opportunities for evaluation. The workstreams will be progressively monitored; consequently the action plan will be flexible and subject to on-going review and possible modification to take account of ongoing developments.

Workstreams:	***Reporting Timeline:***
1. Clinical Exome	*Report 1 – May/June 2019*
2. Whole Exome Trio Analysis	*Report 2 - Nov/Dec 2019*
3. Whole Genome Analysis (Research)	*Report 3 - May/June 2020*
4. Shared Data Repository	*Final Report / Evaluation – TBC*

Management of the work will be through the Scottish Genetics Laboratories Consortium Governance Structure reporting to the Genetics Laboratory Management Committee (GLMC) for the delivery of Clinical Exome Sequencing (workstreams 1) and Whole Exome Trio Analysis (workstreams 2) by the NHSS genetics services providing diagnostic genetic / genomic testing for patients.

Whole Genome Analysis (workstream 3) will be undertaken as part of the continued engagement through the research collaboration with SGP and GeL and will formally report to the SGP Genomics of Rare Diseases Implementation Group (GRDIG).

The work for workstream 4 will be overseen by NSD working collaboratively with NES colleagues implementing the National Digital Strategy reporting to GLMC and GRDIG.

The reporting cycle is based on a December 2018 start date; this was to allow consortium centres to engage with regional procurement and recruitment processes to ensure sufficient allocation of resource in local work-plans to support the achievement of key milestones. Following this it was anticipated that it would take 4-6 months lead in time (as detailed in the breakdown of the reporting cycle below) for the implementation of testing.

In acknowledgement there are insufficient numbers of trained scientists across the UK, recruitment of staff to support the workstreams set out in the action plan has been flexible. Recruited staff will be flexibly trained in order to ensure cover for integrated workflows across the workstreams set out in the action plan.

An overview of each workstream including an update on the first 6 months of the implementation of the bridge funding is set out below.

Workstream 1: Clinical Exome Sequencing (CES)

CES focuses on clinically relevant genes with known associated clinical phenotypes, providing efficient coverage over genes of clinical interest. Although at different stages of implementation the Consortium laboratories have been able to integrate the delivery of CES within a relatively short period of time with modest investment using equipment already available in each Consortium laboratory, and using data analysis pipelines that have been tested and validated.

Based on a December 2018 start date to allow 4-6 months lead in time for (1) the recruitment of additional staff, (2) distribution of work amongst the Consortium laboratories and (3) agreement on testing criteria and requesting process with clinical colleagues, the Consortium laboratories will commence delivery of approximately three CES per laboratory/per week batched effectively for sequencing runs every three weeks with a 112 day turn-around time (TAT) from April/June 2019.

Given that, following the reconfiguration of NHSE laboratories it was anticipated that NHSS may not be able to rely on the provision of testing from out with Scotland, expediting the repatriation of testing provision is exceptionally important to ensure continuity of testing provision for Scottish patients. Therefore the SGLC primarily focused their efforts on identifying send away test requests costing ≥ £450, pursuant of this a 'disease bundling' exercise was undertaken and the bundles allocated to SGLC laboratories for delivery, effectively creating specialist testing centres according to the disease type. See allocations set out in the table below;

Disorder	Number Sent	Percentage of Total Sent	Total No of Genes Analysed	Percentage of Total Genes Analysed
Cancer	25	6.3%	38	0.2%
Cardiac	12	3.0%	580	3.2%
Connective Tissue	13	3.3%	42	0.2%
Hearing Loss	4	1.0%	194	1.1%
Developmental	39	9.9%	514	2.8%
Endocrinology	15	3.8%	65	0.4%
Eyes	46	11.7%	5847	32.1%
Gastrohepatology	1	0.3%	24	0.1%
Haematology	14	3.6%	1118	6.1%
Immunology	5	1.3%	76	0.4%
Metabolic	16	4.1%	388	2.1%
Musculoskeletal Group 1	10	2.5%	140	0.8%
Musculoskeletal Group 2	18	4.6%	189	1.0%
Neurology Group 1	33	8.4%	637	3.5%
Neurology Group 2	75	19.0%	3807	20.9%
Neurology Group 3	32	8.1%	3926	21.6%
Renal	17	4.3%	275	1.5%
Respiratory	14	3.6%	339	1.9%
Rheumatology	5	1.3%	11	0.1%
Total	**394**		**18210**	

Centre	Samples	Percentage	Genes	Percentage
NHS Grampian	85	21.6%	6926	38.0%
NHS Tayside	81	20.6%	2289	12.6%
NHS Lothian	94	23.9%	4622	25.4%
NHS GG&C	132	33.5%	4373	24.0%

It will be vital that the consortium continuously monitor the clinical exome workload and all other workloads to ensure that the laboratories continue to have the capacity to deliver testing.

- **Staff Recruitment to support delivery**

NHS GG&C		NHS Grampian		NHS Lothian		NHS Tayside	
Post	Status	Post	Status	Post	Status	Post	Status
B6 genetic technologist	Recruitment ongoing	B5 genetic technologist	Recruited to post	B6 genetic technologist	Recruited to post	B4 genetic technologist	Recruitment ongoing
B6 genetic technologist	Recruitment ongoing	B6 genetic technologist	Recruited to post				
B7 clinical scientist	Recruited to post	B7 clinical scientist	Recruitment ongoing	B7 clinical scientist	Recruited to post	B7 clinical scientist	Recruitment ongoing
B7 clinical scientist	Recruited to post	B7 clinical scientist	Recruitment ongoing				
B7 genetic counsellor	Recruitment ongoing	B7 genetic counsellor (0.7 WTE)	Retained from SGP	B7 genetic counsellor (0.8 WTE)	Retained from SGP	B7 genetic counsellor (0.5 WTE)	Retained from SGP
Grade 7 Translational Bioinformatician WGS Support (University) – Recruitment pending finalisation of research award for WGS. Grade 7 Project Manager (University) – Contract for existing post holder to be extended pending finalisation of research award for WGS.							

The table above captures recruitment to date across workstreams 1-3.

Regarding the retention of SGP Band 7 clinical scientists; it was initially hoped that these staff contracts could be extended to support the delivery of the additional 500 WGS, relating to the extension of the existing SGP research programme under workstream 3. However, in some cases, these scientists have been subsumed into alternative posts (temporary or permanent) within NHS budgets in the intervening period in order to retain these highly skilled individuals. Therefore some scientists, having previously been employed under SGP, are now engaging with recruitment processes for these posts under the implementation of the bridge to a Scottish strategy for genomics.

The laboratories also have experienced difficulty recruiting to Band 7 clinical scientist, in some instances these posts have had to be re-advertised on multiple occasions. It is considered that this is due to a lack of appropriately trained scientists across the UK. Although the laboratories continue to engage with recruitment processes and have been supported by local HR teams in terms of flexible recruitment (for example NHS GG&C have appointed to a Band 7 post as a development opportunity within the department), the experience has acutely highlighted funding is urgently needed to support the recruitment and training of additional laboratory scientists. This is required not only to cope with current and anticipated demand for genomic testing but also to meet the predicted shortage of highly skilled staff through retirements over the next 5 years.

In reference to the technical posts, some of the laboratories have taken the opportunity to review and revise stock / archive job descriptions to ensure that recruited staff will be flexibly trained in order to ensure cover for integrated workflows across the workstreams.

In the majority of cases clinical genetics support has been retained through the extension of staff contracts for posts recruited for the SGP (see page 13 – *Workstream 3: Continued Engagement with SGP/GEL*).

- **Agreed testing criteria / process to access testing**

A Referral Form for Clinical Exome Testing requests is currently being developed by a consortium short life working group to aid the implementation of a common referral process across Scotland. Requests will be gate kept and clear clinical utility must be demonstrated with clear justification for test at the time the request is submitted before being processed by the appropriate laboratory.

It is the referring clinician's responsibility to ensure informed consent has been obtained and documented for each patient test request. Following extensive discussion at the Genetics Evaluation Panel (GEP) and the Genetics Consortium Steering Group (GCSG) it was agreed that the Record of Discussion form regarding Testing and Storage of Genetic Material compiled by the British Society for Genetic Medicine (BSGM) / Joint Committee on Genomics in Medicine (JCGM) would be used across clinical genetics.

- **Laboratories receiving and sending samples amongst the Consortium according to the agreed allocations**

Two of the four consortium laboratories had implemented a clinical exome service by 1st April 2019. Although all consortium laboratories are able to deliver this work using our existing NHS equipment, NGS processes and infrastructure they are at differing stages of validation / implementation of CES, this has been largely due to time taken to recruit staff to support delivery and regional variation as to information governance for bioinformatics pipeline analysis and data storage.

NHS GG&C

- The West of Scotland Laboratory will complete validation by the 3rd of June 2019.
- The bioinformatics analysis pipeline and IT infrastructure is in place and will be sufficient to enable clinical exome data storage for at least 12 months.
- Information governance has proven challenging and the laboatory is currently working through the information governance approval process. It has been estimated that this will be fully in place within the next 3 to 6 months

NHS Lothian

- The laboratory has reported that it is currently able to deliver CES using existing NHS NGS processes and infrastructure and have the capacity in house to run this volume of tests following a successful pilot
- The laboratory has started receiving test requests and is currently in negotiation with clinical colleagues regarding panel composition

NHS Grampian & NHS Tayside

- NHS Grampian and NHS Tayside are delivering a clinical exome service using commercial solutions for bioinformatic pipeline analysis, it is noted that arrangement with commercial provided ordinarily allow for a fixed term data storage (approximately 2 years) included in the costs for data analysis.
- Although both laboratories have secured local data storage to accommodate clinical exome sequence data on local servers, this will fill rapidly and there will be a need for additional storage capacity which is currently procured on a piecemeal basis regionally at costs which vary drastically. This position is not sustainable given the volume of data the laboratories will generate and are required to store.
- It is also noted that local information governance permissions are in place to allow the laboratories to access external service providers.

- **Estimated 48 clinical exomes sequenced by mid May 2019 - Tracking/monitoring turn-around time (TAT) / costs of service delivery against equivalent sendaway spend / recording the detection rate of clinically significant genetic variants (diagnostic yield).**

The Consortium laboratories have agreed a turnaround time for clinical exome sequencing of 112 calendar days. Performance against this time will be reviewed regularly and reduced if clinically appropriate and pragmatically feasible. The laboratories will work with clinical colleagues to prioritise samples due to clinical urgency so that patients receive results as soon as possible.

Although a standardised Referral Form for Clinical Exome Testing requests is currently being developed to aid the implementation of a common referral process across Scotland, two of the laboratories have started to receive requests locally and following engagement with requesting clinicians, where appropriate have started to process these;

- The laboratories have sequenced 43 samples using the clinical exome. All samples have been referred by local clinical colleagues.
- Data analysis and interpretation has been completed for these 40 samples; any variants that require confirming have been checked by Sanger sequencing.
- 3 samples received have been received and are being processed / undergoing analysis for metabolic referrals.
- To date 18 reports have been issued.

Report 2 - Nov/Dec 2019:

Although information is being collected there is currently insufficient data as to turn-around time (TAT), costs of service delivery against equivalent sendaway spend and detection rate of clinically significant genetic variants (diagnostic yield) to provide illustrative results. It is anticipated that by the issuance of the subsequent report, all four laboratories will be delivering CES the laboratories will have amassed sufficient data for meaningful analysis in the performance monitoring areas.

Workstream 2: Whole Exome Sequencing (WES)
The implementation of WES offers the potential to achieve a diagnosis for patients presenting with severe developmental disorders including congenital anomalies, neuro-developmental disorders, abnormal growth and dysmorphic features. Trio analysis (usually an affected child and their parents), replicating processes developed and successfully implemented within the Deciphering Developmental Disorders (DDD) study / DECIPHER, will enable the rapid implementation of familiar and evidence-based systems for recording phenotypic information, filtering of plausibly diagnostic variants and report generation.

Where a diagnosis cannot be achieved through the application of WES the step wise nature of the bridge funding offers the opportunity for patients to be put forward for whole genome sequencing (WGS) where appropriate, thus offering an additional opportunity for the evaluation of the value of WGS for the delivery of front line patient care.

The WES service will be provided by NHS Lothian laboratory and are set out to provide diagnosis for 300 patients (900 samples) per year, assuming optimal batching of 96 samples per run (or 31 trios) for 1 sequencing run every 5 weeks, on average 9-10 per year.

Based on a December 2018 start date and allowing 4-6 months lead in time for recruitment, procurement and ensure work has started to get requisite information governance is in place.

- **Procurement of work station and arrangements for reagents/consumables (purchase/rental) complete**

Reagents for library preparation and hybridisation capture for the first year of the WES project were purchased at the end of the last financial year. The laboratory has been validating identical reagents manually and extensively for existing gene panels and is getting extremely high quality data consistently. It is anticipated that the step up to whole exome testing will be straightforward from a technical point of view however the laboratory is still to complete procurement of a liquid handler designated for this workstream to fully implement the automated solution.

An automatic liquid handler tender has been released (National procurement under framework agreements) and returns were due in early May 2019. The successful bidder should be able to place instrument during July / August.

Hybridisation probes for the whole exome capture are out to competition, which closed on Monday 20th May.

- **Service agreement in place with provider for WES**

Hybridisation capture libraries prepared at the laboratory will be sequenced by Edinburgh Genomics. An SLA is in the final stages of negotiation between NHS Lothian and the University of Edinburgh.

The procurement of suitable bioinformatic pipeline analysis to support this workstream is subject to ongoing discussions.

- **Consent documentation finalised**

The patient recruitment process has been agreed with local consultant geneticists and has been discussed more widely within the consortium. As previously noted combined "*Request and Record of Discussion*" form has been produced based on BSGM guidelines and has been sent out for comment and ratification by consortium clinicians.

- **Information governance in place including engagement with Public Benefit and Privacy Panel for Health and Social Care (PBPP) and/or local Caldicott approval processes as appropriate**

Regarding data handling issues; a proposal covering all aspects of data handling has been submitted to NHS Lothian local Caldicott Guardian in January 2019. Further information was requested and submitted late March 2019. Laboratory colleagues are still awaiting a response. In conjunction with other consortium colleagues a PBPP application is nearing completion and will be submitted with a view to achieving a national solution.

- **Staff recruitment to support delivery**

As previously noted the allocated Clinical Scientist (Band 7) has been recruited to post and interviews for the Senior Genetic Technologist (Band 6) post were recently completed, the position has been offered to the preferred candidate.

- **Commence patient recruitment/consenting process**

Clinicians are ready to start submitting family trios for testing.

Clinical colleagues have also expressed a desire to continue utilising the DECIPHER database. At this stage they have considered that there is no other viable alternative solution of this quality for the storage of developmental delay NGS results with interfaces and tools for recording and cross referencing patient phenotypes and variants. This has proven invaluable for MDT meetings; particularly where the submitting clinicians are geographically distant. The easy availability of the historic DDD cohort WES results in combination with extensive clinical information for comparison purposes remains the most powerful approach.

Links between the Edinburgh molecular genetic / cytogenetic teams and DECIPHER are longstanding and productive. The Edinburgh team is in regular communication with the database curators and are exploring any useful improvements for this project.

Continued use of DECIPHER in an NHS setting will be subject to ratification of afore mentioned information governance requirements

Report 2 - Nov/Dec 2019:

Delays to the proposed timeline for implementation associated with engagement with requisite procurement and data governance processes are beyond the immediate control of NHS Lothian laboratory colleagues / management.

However the service is confident that once information governance requirements are satisfied and procurement of equipment and services are in place they should be in a position to commence trio WES and analysis in July 2019.

It is anticipated that the next report will contain an update of the implementation of sequencing and pipeline analysis processes. Recruitment of patients / families will have commenced in earnest and approximately 3 sequencing runs will have been completed and undergoing analysis.

Workstream 3: Continued Engagement with SGP/GEL
This builds upon the ongoing work of the Scottish Genomes Partnership (SGP) project exploring Scottish participation in the Genomics England 100,000 Genomes Project.

SGP is a Scotland-wide collaboration between the four Scottish University medical schools and NHS Scotland. SGP builds on the successes of previous pan-Scotland academic research initiatives in the field of genetics (e.g. Generation Scotland), long-standing national working across the NHS Scotland Regional Genetics Services, and pre-existing clinical academic relationships within the Scottish genetics/genomics community.

The main aim of the project collaborating with Genomics England on Scottish participation in the 100,000 Genomes Project is to assess the utility of whole genome sequence tests for the diagnosis of rare inherited disorders in patients where routine genetic testing had not identified a cause for their condition. Scottish participation in the 100,000 Genomes Project operates under separate regulatory approvals to the rest of the UK. The research study protocol supports diagnostic analysis by Genomics England, development and use of diagnostic analysis pipelines within Scotland, and access to data for research purposes via Genomics England's research environment.

SGP – Phase 1
The evidence base on which to assess the utility of whole genome sequence tests has started to accumulate as we approach the end of the first phase of funding for this project ("SGP1"). All processes developed for SGP1 will continue to be used as we extend into the second phase of work described within the Genomics Implementation Plan. The results that are starting to emerge from SGP1 are summarised below.

- Complete data for 999 individuals from 395 families have been submitted to Genomics England for analysis.
- From these 395 families, results from Genomics England analysis have been made available to NHS clinical genetic laboratory scientists from 352 families. Results from the remaining families are expected within the next 3 months.
- NHS laboratory scientists have performed an initial assessment of results for 195 families. From among these, 59 new diagnoses have been identified. NHS genetics clinics are in the process of confirming these findings before returning these results to families.
- A process has been agreed for more detailed inspection of results for those families where no diagnosis was made after the initial assessment. The yield of additional diagnoses from this more detailed assessment will be monitored, and outcomes used to inform future approaches to assessment of results from Genomics England analysis.
- Local (within-Scotland) analysis pipelines have been developed for those families recruited with a diagnosis of developmental delay. This will be applied in relevant families where no diagnosis is made from Genomics England results, and the additional yield from this pathway will be monitored.

The main challenge for this work is in the ongoing interpretation and reporting of results to families by the NHS Regional Genetics Services, in addition to their routine diagnostic workload, beyond the end of SGP1 funding. This work will continue from SGP1 into "SGP2", with staff posts in NHS genetics laboratories and clinics across Scotland extended (via CSO) through the Genomics Implementation Plan as an extension of the existing SGP research collaboration.

SGP – Phase 2 (Bridge Funding)
SGP2 also includes sequencing and analysis of a further 500 whole genome sequences, using the same funding mechanism noted above. This work is subject to complex multi-organisational agreements and regulatory approvals, all of which require to be updated to reflect the outcomes of negotiations with Genomics England.

At the end of 2018, Genomics England – in collaboration with the NHS in Scotland, England, Wales and Northern Ireland – completed sequencing of the 100,000th genome as part of the 100,000 Genomes Project. As a result of this, recruitment into "the 100,000 Genomes Project" (as it has been known until now) was closed across the UK.

During 2019, NHS England will transition whole genome sequencing from “research-first” to “clinical service-first” within a re-configured Genomic Medicine Service (GMS), building on the processes developed as part of the 100,000 Genomes Project. Within the GMS, NHS England will commission whole genome sequencing from Genomics England as a routine test for a defined list of disorders, and analysis will follow the same pathways developed for the 100,000 Genomes Project. The technical infrastructure at Genomics England will change as part of this, though will still operate to at least the same data security and governance standards as for the 100,000 Genomes Project.

Negotiations between SGP and Genomics England regarding ongoing and future working relationships have been taking place since December 2017, with limited progress. Genomics England are currently prioritising the development work required for roll-out of the GMS and delivery of the National Genomics Informatics Structure (NGIS) required to underpin this. As a result, they have been unable to dedicate resource to develop a version of NGIS that is compatible with the research approvals in place for Scottish participants. In lieu of this, Genomics England will maintain the existing technical systems developed for the 100,000 Genomes Project until around the end of 2019 (date still subject to internal discussions within Genomics England). Beyond this, it is not clear what Genomics England systems will be available to Scotland, and whether these can be modified to align with Scottish regulatory approvals.

Due to the protracted nature of the ongoing negotiations with Genomics England, progress against objectives is as follows:

- **Staff contracts extended (following SGP) / Staff Recruitment to support delivery complete**
  The extensions to NHS posts are currently being finalised within the four NHS regional genetics services. The research award from CSO for SGP2 will be finalised during June 2019, and extension of the translational bioinformatician and project manager posts will then be arranged.

- **Concluded discussions with GEL regarding additional genomes submitted by SGP**.
  As described above, an interim solution is now in place until the end of 2019. Discussions are ongoing with Genomics England about systems beyond this, which will include an opt-out in the event that Genomics England are unable to deliver a suitable alternative within 2-3 months of closing existing systems. Meantime, local analysis capabilities continue to be developed as an enhancement or alternative to the Genomics England analysis pipeline.

- **Public Benefit and Privacy Panel for Health and Social Care (PBPP) and Research Ethics Service Committee (REC) amendments submitted and approvals in place.**
  Amendments were submitted at the beginning of June, following agreement by Genomics England to maintain existing systems until the end of the year. Further amendments will be required at such time as these systems are replaced by alternatives.

- **Resume recruitment for whole genome analysis according to criteria for a refined list of disorders.**
  Recruitment will resume once regulatory approvals are in place, which is currently expected around August 2019. Clinic sites have resumed screening in patients in readiness for this.

- **Amendment/replacement of the existing multi-organisational agreements is also required to support delivery of this work, and work has started on this.**

The main challenge for delivery of this work relates to the ongoing relationship with Genomics England. Plans for local analysis are in place and will be further developed during the funding period to ensure that all 500 genomes can be analysed and reported in the event that Genomics England are unable to provide a suitable replacement for 100,000 Genomes Project systems. These local analysis pipelines will also be evaluated alongside the Genomics England pipeline.

Plans for a health economic evaluation of whole genome sequence tests versus whole exome testing and standard genetic testing pathways have also been developed as part of SGP1. A separate funding

application, aligned with the deliverables within this Implementation Plan, has been submitted to CSO and we await the outcome of this.

Work to understand genomic test penetrance by geographic region, demographic and socioeconomic status is also in the early stages, enabled by study participants consenting to record linkage via CHI. Separate funding will also be required to support this work.

The SGP2 research funding from CSO will now also include £4,000 to run two in-person meetings with staff from NHS regional genetics services, IT & governance and SGP academic groups, where attendees will present their experiences of implementing and delivering whole genome sequence testing during SGP1 & SGP2. Outcomes from these meetings will include collection of case studies, and identification of challenges/solutions for a potential transition of genome testing from research to service.

Report 2 - Nov/Dec 2019:
By report 2, we expect to have all regulatory approvals and contracts in place and to have resumed recruitment for whole genome sequence testing. Assessment of numbers recruited, sequenced, analysed and reported will continue as for participants in SGP1, along with an initial evaluation of diagnostic yield by clinical condition. We will also know whether the health economic work has been funded; and be able to report on progress with developing record linkage to assess test penetrance.

Workstream 4: Shared data repository
As previously noted laboratories have secured local data storage to accommodate exome sequence data on local servers for the immediate future, but this will fill rapidly and there will be a need for additional storage capacity which is currently procured on a piecemeal basis regionally at costs which vary drastically. This position is not sustainable given the volume of data the laboratories will generate and are required to store.

The implementation of routine genomic testing with adequate data storage and informatics support for clinical care facilitated by a cross-board system for electronic test requesting, sample sharing and result reporting are of the utmost importance for the realisation of Precision Medicine for patient care in NHSS. The SGLC and NSD have recognised this and are currently engaging with NES colleagues who are tasked to implement key elements of the 2018 Digital Health & Care Strategy; discussing potential collaboration around the National Digital Platform (NDP) and Genomics in order to contribute to the delivery of genetic laboratory services for the future.

The development of a dedicated shared data repository within NHS Scotland will standardise the storage of genomic data and identified variants that is currently lacking in the Consortium laboratories. Furthermore, in order to maximise the potential of sequencing analysis, data sharing between the four laboratories is essential to allow accurate and consistent interpretation of identified variants. The Consortium will also seek to ensure that a shared data repository will have the capability of linking with similar NHS repositories elsewhere in the UK to further facilitate the clinical interpretation of genomic data, and available as a potential resource for approved research under appropriate controls.

Preliminary discussions with NES / NDS colleagues around the National Digital Platform and the development of data architecture required by the consortium for centralised genomic data storage have been positive, and work has recently commenced in earnest;

- ✓ NES / NDS colleagues have secured resource for the provision of senior support for 6-8 days on a consultancy basis to undertake target architecture work to initiate architecture development for the genomics data store project. This is an interim resource intended to kick-start project.

- ✓ Individual laboratory conversations have been scheduled (June 2019) to initiate data scoping work; to understand the technical and workflow aspects of current model/s across the laboratory sites required to compile possible technical architecture solutions

- ✓ It is anticipated that by the end of July 2019 the culmination of data scoping work will allow 1-3 possible technical architectures to be drafted for consideration by the consortium.

- ✓ The intention is for longer term support for the project to be provided by a Data Architect role. The job description for this post has been approved and will be the first Data Architect in NES, it is anticipated that this post will go out to advertisement in July 2019.

At these early stages of the collaboration we work is primarily focusing on the establishment of a secure centralised data repository that is accessible across the SGLC sites and is scalable to support /store the increasing volume of genetic / genomic data that will be produced in the coming years.

Report 2 - Nov/Dec 2019:
It is anticipated that by second report a Data Architect will have been appointed to post, the consortium will have agreed upon data architecture for genomic data within the NDP and steps towards implementation will have been initiated including engagement with regional eHealth leads.

Profiled Costs: Across all four centres and all test types

TOTAL COST		£ 4,237,363	N diagnoses		
	CE-specific	*£ 312,500*	*625*	*250 singletons per year*	
	WES-specific	*£ 986,190*	*750*	*300 trios per year*	
	WGS-specific	*£ 803,240*	*200*	*150 trios plus 50*	
	Shared costs (excl staff)	*£ 393,750*			
	Staff costs (shared)	*£ 1,741,683*			

			Financial year			
			2018-19	2019-20	2020-21	Total
SALARY - WGS, WES and clinical exomes			£ 108,690	£ 769,498	£ 863,495	**£ 1,741,683**
	Band (AfC) / Grade (Uni)	FTE				
Project Manager (University)	7 (Uni)	1	(from SGP)	45,027	63,439	108,466
Clinical Genetics Nurses	7 (AfC)	3	(from SGP)	111,313	155,838	267,151
Laboratory Genetics Scientists	7 (AfC)	8	(from SGP)	395,779	415,568	811,346
Genetic technologist	6 (AfC)	4	78,672	157,344	165,211	401,227
Translational Bioinformatician (University)	7 (Uni)	1	30,018	60,036	63,439	153,493
NHS LABORATORY CONSUMABLES, COMPUTING & EQUIPMENT			£ 281,148	£ 449,230	£ 456,630	**£ 1,187,008**
IT and Software			37,500	75,000	75,000	187,500
Travel and meeting costs			1,250	2,500	2,500	6,250
WGS - DNA extraction & quantification, 2D tubes				4,520	6,720	11,240
Consumables for laboratory validation - WGS			-	10,400	15,600	26,000
WES set-up costs			63,993	-	-	63,993
WES - Kits			58,327	116,654	116,654	291,635
WES - Other costs (quanitifcation, tips, confirmations etc)			22,500	45,000	45,000	112,500
WES - Bravo NGS workstation			35,078	70,156	70,156	175,390
Clinical exomes - includes DNA extraction, NGS, analysis and storage			62,500	125,000	125,000	312,500
SEQUENCING & ANALYSIS - mainly WGS			£ 68,535	£ 543,169	£ 696,969	**£ 1,308,673**
WES at Edinburgh Genomics			68,535	137,069	137,069	342,673
Centralised data storage			-	100,000	100,000	200,000
WGS at Edinburgh Genomics			-	170,000	255,000	425,000
Genome assembly - Genomics England			-	30,000	45,000	75,000
Genome annotation & storage - Genomics England			-	93,600	140,400	234,000
Genome annotation - EPCC analysis compute			-	3,100	5,400	8,500
Genome storage - EPCC, 3 years			-	9,400	14,100	23,500

Gantt Chart

									Report 1						Report 2						Report 3						Evaluation		
	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21
CE	Preparatory Time		Lead in Time for Procurment/ negotiations with SGP/GEL																										
WES																													
WGS									x	x	x																		

Delays in recruitment have resulted in an under spend on staff at the early stages of bridge implementation. This under spend has been mitigated to some extent through bulk purchase if consumable at an early stage of the bridge, ensuring that resources are in place for validation and initial stages of service delivery.

Concluding Comments

The first six months of implementation of the bridge to a Scottish strategy for genomics has seen the laboratories make steady progress towards laying the foundations for the delivery of genomics testing in an NHS setting. However hurdles are still being negotiated; difficulties encountered when engaging with recruitment, procurement, information governance and collaborative working with colleagues from industry and academia have been met across the consortium laboratories and exemplifies the difficulties working across health board boundaries frequently encountered by the consortium.

Delays associated with the recruitment and retention of staff demonstrates the lack of appropriately trained scientific and clinical staff to support the expanding workload associated with the implementation of genomics for the delivery of precision medicine.

The application of information governance rules has been associated with varying levels of bureaucracy depending on regional variations of application. This severely hinders cross board communication not only between laboratory sites in sharing genomic data, analysis and reporting but also potentially valuable collaborations with academic and industry colleagues not only for research but also for the delivery of clinical care for NHS patients. This is particularly visible when engaging with Edinburgh Genomics for the procurement of sequencing runs, difficulties encountered with continuing collaboration with Genomics England and engaging commercial providers for pipeline analysis accessible by laboratories across the UK as part of the 100,000 Genomes Project.

It would be advantageous if the strategy for the implementation of genomics for Scotland could take these challenges into account and where possible seek to promote working across health board and UK boundaries. Sharing data and analytics will be imperative to realising the true potential of genomics medicine.

Going forward the laboratories and clinical colleagues will continue to work closely with each other and within SGP to ensure that the genomics services implemented under the bridging initiative will be developed to maximise patient benefits and will provide a basis for future advancements in the area of genomics. As the initial implementation phases of CES / WES near completion and the laboratories move into routine delivery of service for patients, and as WGS continues as a research track as part of SGP, it is anticipated that successive progress reports will add to the accumulating body of evidence around genomic testing that can be considered alongside knowledge shared from the work of other UK and international projects.